behavioral outcomes in children have been reported as part of the Ottawa Prenatal Prospective Study (OPPS)."

"[I]n both the work arising form the OPPS and studies from other laboratories, one of the most consistent neurobehavioral findings is an association between maternal cigarette smoking and poorer performance by children on subscales of global tests that assess the verbal domain and specific language/auditory tests. To extend and further examine these observations, the present work investigates whether exposure to cigarette smoke during fetal development is related to central auditory processing in 6 to 11-year olds participating in the OPPS. Considerable background prenatal and postnatal demographic information, as well as a detailed history of drug use during pregnancy has been collected from the participating women. Furthermore, in the present work an attempt has been made to examine the role of prenatal and postnatal secondary smoke on central auditory processing in children."

"An OPPS Passive Smoke Exposure Questionnaire assessed passive exposure of the child for three different time periods. Exposure of the mother to secondhand smoke during pregnancy was recorded in typical number of hours per week and represented the sum of separate assessments of week and weekend exposure both at home and at work; the child's passive exposure at birth and yearly thereafter was similarly estimated in typical number of total hours per week that the child was in the same room as a smoker (home or elsewhere) during both the week and weekend; the child's passive exposure for the week previous to testing was described in detail and included the time and number of hours for the most recent exposure."

"The incidence of auditory problems (including otitis media) was not associated with maternal smoking or with the child's exposure to secondhand smoke."

"The creatinine-corrected cotinine values were positively correlated with the reported passive exposure of the child in the 3 days previous to testing and negatively correlated with the time interval between the last recalled smoke exposure period and the time of the urine collection."

"[T]he deficits noted in the present work suggest that in utero exposure to smoke affects fundamental aspects of auditory processing -- ones which may manifest themselves as impaired performance on auditory-based cognitive and memory tasks."

"It is noteworthy that the correlation between the parental report and the biological marker was less when nonresidential sources of smoke exposure were excluded from the exposure estimate indicating the importance of considering outside-the-home sources of passive smoke when evaluating second-hand smoke effects."

"Previously published results from the OPPS sample revealed that on tests of speech and language skills, the performance of 6- to 9-year old children born to nonsmoking women exposed to passive smoke during pregnancy was between that of children born to heavy active smokers and nonsmokers. In a similar fashion, in the present work the children of nonsmoking women exposed to second-hand smoke either in utero or after birth have average scores on both the Competing Words subtest and the Composite Score that were very similar to those of the children born to women characterized as light smokers during their pregnancies. Although not statistically significant, the average scores on Competing Words and the Composite Score for this passively exposed group were lower than for the nonexposed group. Although based on a small sample, the data suggest that prenatal passive smoke exposure does not add to the effects of active smoking but passive smoke exposure (either in utero or after birth) may contribute to an effect in children born to nonsmokers. Whether this is a spurious observation or whether it reflects that the consequences of heavy active smoking are not potentiated by additional passive exposure remains to be investigated. Note that in a study examining passive smoke exposure during pregnancy and birthweight, passive smoke exposure was significantly related to low birthweight among maternal nonsmokers but there was no additive effect of passive smoking among those women who were active smokers."

"Although extensive measures of passive smoke exposure were taken, the data have to be interpreted with considerable caution. There are numerous variables above and beyond the quantity smoked by those in the presence of the pregnant woman or the child that determine the actual exposure of the second-hand recipient. These include the proximity of the active smoker to the passive recipient, the nature and extent of the ventilation in the physical environment and the accuracy of recall."

"Among the implications of these findings is that impairments in auditory processing related to smoking result in difficulties in the perception of speech when auditory conditions are not optimal. At the age of the children examined in the present work, such a situation frequently arises in the classroom setting. The consequences to the child with impaired auditory processing capabilities may be reflected in difficulties in learning and behavior that have been linked to in utero exposure to cigarettes."

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[9] **Mitchell, E.A., Brunt, J.M., and Everard, C., "Reduction in Mortality from Sudden Infant Death Syndrome in New Zealand: 1986-92," *Archives of Disease in Childhood* 70: 291-294, 1994 [Issue 83, Item 33]**

The authors of this paper report that postneonatal and SIDS deaths decreased following the institution of a national program aiming to decrease the frequency of infants sleeping prone, maternal smoking, lack of breast feeding, and infants sharing a bed with another person.

EXCERPTS:

"Mortality from sudden infant death syndrome (SIDS, or cot death) in New Zealand has been high by international standards (4/1000 live births). Within New Zealand the rate is higher in Maori than in non-Maori (predominantly European infants) and higher in South Island than in North Island. The National Cot Death Prevention Programme aims to reduce the prevalence of four modifiable risk factors for SIDS, namely infants sleeping prone, maternal smoking, lack of breast feeding, and infants sharing a bed with another person."

"The aim of this paper is to describe the changes in total postneonatal and SIDS mortality in New Zealand from 1986 to 1992."

"Total mortality decreased dramatically in 1990 and has continued to decrease in 1991 and 1992. The decrease has been greater in non-Maori than in Maori groups."

"The Cot Death Prevention Programme initially targeted three risk factors; prone sleeping position, smoking in pregnancy and around the infant in the first year of life, and bottle feeding. In 1992 a fourth message was added: 'do not sleep with your infant.' Breast feeding rates in New Zealand are high compared with the United Kingdom and will be difficult to improve. Maternal smoking rates are difficult to change and have not changed over this time period. There is some evidence to suggest that the prevalence of bed sharing has decreased slightly."

"The decrease in mortality from SIDS has been dramatic."

[10] **Otitis Media Guideline Panel, "Managing Otitis Media with Effusion in Young Children," *Pediatrics* 94(5): 766-773, 1994 [Issue 86, Item 35]**

As part of a clinical practice guideline, this document includes advising parents not to smoke around children among its recommendations for managing otitis media with effusion.

EXCERPTS:

"This reference guide contains highlights from the *Clinical Practice Guideline, Otitis Media With Effusion in Young Children.* The Otitis Media Guideline Panel, a private-sector panel of health care providers, developed the *Guideline* after comprehensively analyzing the research literature and current scientific knowledge of the development, diagnosis, and treatment of otitis media with effusion in young children."

"Longitudinal studies of otitis media with effusion show spontaneous resolution of the condition in more than half of children within 3 months from development of the effusion. . . . The likelihood that middle ear fluid will resolve by itself underlies the recommendations made for management of otitis media with effusion."

"Scientific evidence showed that the following environmental factors may increase potential risks of getting acute otitis media or otitis media with effusion:"

"Bottle-feeding rather than breast-feeding infants.
Passive smoking.
Group child-care facility attendance."

"Because the target child for Guideline recommendations is beyond the age when the choice of breast-feeding versus bottle-feeding is an issue, this risk factor was not considered at length."

"Passive smoking (exposure to another's tobacco smoke) is associated with higher risk of otitis media with effusion. Although there is no proof that stopping passive smoking will help prevent middle ear fluid, there are many health reasons for not exposing persons of any age to tobacco smoke. Therefore, clinicians should advise parents of the benefits of decreasing children's exposure to tobacco smoke."

[11] **Warburton, D.M., "Environmental Nicotine and Behavior." In: *The Vulnerable Brain and Environmental Risks, Volume 3: Toxins in Air and Water.* R.L. Isaacson and K.F. Jensen (eds.). New York, Plenum Press, 153-166, 1994 [Issue 87, Item 37]**

In this review, the author discusses whether airborne nicotine levels related to ETS could possibly produce the behavioral effects attributed to nicotine from active smoking.

EXCERPTS:

"Nicotine can enter the body by inhalation of air containing tobacco smoke, by absorption of nicotine through the skin from smoke particles adhering to the epidermis, and from some vegetables in the diet. Idles (1990) pointed out that nicotine is not as tobacco-specific

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as it is commonly thought to be. Significant concentrations of nicotine are present in eggplants, green peppers, potato peel, teas, and tomatoes. In view of these sources of nicotine, some care must be taken when extrapolating from measurements in body fluids of cotinine, the major metabolite of nicotine, to cigarette exposure when there are low levels of exposure to nicotine, as in ETS."

"In comparison with gases in ambient air, the levels of nicotine in the air are subject to considerable variation, which makes estimation of exposure to nicotine in environmental tobacco smoke (ETS) difficult."

"Many monitoring studies have measured levels of nicotine, particles, and other substances in a variety of environments and in many parts of the world. In offices, restaurants, and public facilities where smoking is allowed, the level of nicotine in the air typically has ranged between 2 ug/m^3 and 20 ug/m^3."

"The nicotine levels that have been found in even the 'smokiest' environments (such as bars) are many times below occupational exposure limits."

"From the personal monitoring study, it can been seen that the issue of personal exposure is complex; it is not possible to extrapolate from a single location measure to the personal exposure of an individual. Consequently, it is an empirical question whether a correlation exists between environmental exposure and the amount of nicotine absorbed in the body."

"[C]aution must be exercised when estimating nicotine exposure from measurements of urinary cotinine in body fluids, when the person is exposed to low levels of nicotine, such as those associated with ETS exposure. As a result, estimates of exposure have been attempted from the nicotine levels in body fluids."

"Estimates of nicotine exposure have revealed very low levels of nicotine in the serum of nonsmokers who have been exposed to cigarette smoke. Nonsmokers in a poorly ventilated bar achieved plasma nicotine levels of 2.3 ng/ml and 3.9 ng/ml in a smoke-filled, unventilated room. This amount would be equivalent to the serum levels achieved by one or at the most two puffs on a cigarette by a smoker."

"In this section, I will show that nicotine has beneficial effects on mood and performance. Thus, the question that must be answered is whether the amount of nicotine taken in by a nonsmoker from ETS could have any effect on behavior. The relevant evidence is the determination of threshold plasma levels of nicotine that must be exceeded for behavioral effects to be produced."

"From these data and those of smoking, it would seem that the threshold dose is in excess of 10 ng/ml for calming effects and over 14 ng/ml for happiness increases."

"[T]hese serum nicotine levels are not achieved with ETS exposure in normal workplace environments. Only in the most extreme laboratory situations of a large number of cigarettes smoked and no ventilation would these levels be approached. However, with these levels of exposure, the annoyance from the ETS would far outweigh any marginal mood enhancement by nicotine."

"[I]t would seem that simple processing is improved by nicotine doses in excess of 14 ng/ml. Once again, these levels would not be exceeded by workplace exposure."

"[I]t would seem that complex processing is improved by nicotine doses in excess of 6 ng/ml, levels that are still in excess of the maximum environmental levels of nicotine exposure of 2.3 ng/ml and 3.9 ng/ml in a smoke-filled, unventilated room. The finding of thresholds for behavioral effects in this section fit with other physiological data. The 2.0 mg dose of nicotine (buccally absorbed), which improved vigilance and . . . performance, increased heart rate by a mean of 6 beats/min. On the other hand, normal, healthy adult men and women who were exposed to ETS for periods up to 2 hr under resting or exercise conditions had no significant changes in heart rate or blood pressure."

"The evidence from this section shows that nicotine can improve processing capacity. The effects on smokers and nonsmokers can be seen with venous plasma nicotine levels of as little as 8 ng/ml. These threshold values were smaller than those that seem to be required to produce mood changes, a finding that suggests that different neurochemical systems mediate the mood and performance effects."

"Despite the much lower threshold levels for information processing, these levels are 2-3 times the levels of 2.5 ng/ml found in nonsmokers exposed to ETS for 2 hr in a very smoky bar. From these data, it seems unlikely that environmental nicotine can modify information-processing positively or negatively in everyday environments. Only with extreme indoor environments are any effects possible, assuming that the person can tolerate the smoke."

"In summary, we are looking for an effect at nicotine doses that could be described as the equivalent of expecting a drinker to show an effect from consuming a Manhattan cocktail made in the proportion of a thimbleful of whisky added to an Olympic-size pool of dry vermouth."

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ETS Exposure and Monitoring

[1] **Apseloff, G., Ashton, H.M., Friedman, H., and Gerber, N., "The Importance of Measuring Cotinine Levels to Identify Smokers in Clinical Trials,"** ***Clinical Pharmacology and Therapeutics*** **56: 460-462, 1994 [Issue 86, Item 36]**

This paper reports on the results of cotinine screenings to validate the nonsmoking status of persons volunteering to participate for clinical trials. Based on their data, the authors concluded that some 16 percent were "tobacco users," despite their self-reported nonsmoking status.

Excerpts:

"The purpose of the current study was to examine the reliability of a personal history in determining tobacco use among volunteers in phase I clinical trials designated to exclude smokers."

"In screenings . . . 11 of 41 volunteers (27%) tested positive for urinary cotinine, with levels as high as 2960 ng/ml. This indicates that the percentage of smokers who might have been enrolled in a clinical trial for nonsmokers was greater than that in the general population."

"In total screenings of 282 purported nonsmokers, 45 tested positive for cotinine (16%). It is likely that an even higher percentage were positive for cotinine because the . . . assay used at the southwestern facility was reliable only for levels above 1000 ng/ml, even though 500 ng/ml was reported . . . as the cutoff. Clearly it is highly probable that a more accurate assay would have shown that even a larger percentage of subjects screened were tobacco users."

"Our findings show that subjects volunteering for clinical trials cannot be relied on to provide an accurate history of tobacco use and should be screened for cotinine in their urine not only before the beginning of a study but also after any outpatients periods."

"Unfortunately, using a cutoff of 500 ng/ml, investigators will likely accept into their studies smokers who have abstained for only 1 day or less, whereas a cutoff of 50 ng/ml has a sensitivity of 97% and a specificity of 99%."

"Researchers have reported nicotine in a variety of foods, including tomatoes, potato peels, eggplants, green peppers, green tea, and some brands of instant tea, but the levels of urinary cotinine resulting from consumption of these will not usually be elevated above 50 ng/ml unless large quantities are consumed."

"We were able to reexamine the results from Ohio using a cutoff of 50 ng/ml rather than 500 ng/ml, and five additional subjects of the 41 screened tested positive, for a total of 39%. One additional subject of the 15 tested at admission was positive, for a total of 13%, and four of 19 subjects (21%) in the two ongoing studies tested positive."

"Considering the unreliability of personal histories, the potential effects of tobacco on pharmacokinetics and pharmacodynamics, and the adverse effects of acute withdrawal from smoking, we believe drug development programs should measure urinary cotinine levels and use an upper limit of 50 ng/ml to avoid enrolling smokers inappropriately in phase I trials."

[2] **Bermudez, E., Stone, K., Carter, K.M., and Pryor, W.A., "Environmental Tobacco Smoke Is Just as Damaging to DNA as Mainstream Smoke,"** ***Environmental Health Perspectives*** **102: 870-874, 1994 [Issue 86,Item 37]**

These authors report that solutions of sidestream smoke "tar" induced "nicks" in the DNA of animal cells exposed *in vitro*, and postulate that this might be related to the claimed carcinogenic properties of ETS.

Excerpts:

"We now report studies that show the tar component in sidestream smoke produces DNA nicks in viable mammalian cells. We also report the effects of reduced glutathione (GSH), catalase, superoxide dismutase (SOD), diethylenetriamine pentaacetic acid (DTPA), and deferoxamine on the yield of DNA nicks caused by ETS tar solutions."

"For this study, tar from the sidestream smoke of 2R1 research-grade cigarettes was collected . . . and extracted . . . These solutions were used as a model of ETS tar because sidestream smoke makes up at least 85% of the ETS. Our results show that ETS tar solutions can cause DNA nicking in viable mammalian cells; to our knowledge, this is the first report of the DNA nicking capability of tar from ETS."

"Both mainstream tar solutions and ETS tar solutions produce hydrogen peroxide with a time dependency. Mainstream tar solutions produce 15 times more H_2O_2 than ETS tar solutions."

"[T]ar from either mainstream smoke or ETS can enter a cell and associate with DNA. Since alveolar macrophages were used and these cells are not associated with lung cancer, we cannot infer a relationship between the DNA association observed in these experiments and the carcinogenicity of cigarette tar."

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"Environmental tobacco smoke tar solutions cause DNA nicking in these viable rat thymocytes. Previous tests of DNA damage were done using cigarette smoke or tar solutions from mainstream smoke."

"Even though these studies do not assess direct damage to DNA caused by ETS, [it] is clear that components of ETS are genotoxic. As mentioned before, to our knowledge, this is the first report of the DNA-damaging capability of tar from ETS."

"Our results with ETS tar solutions are similar to those obtained with aqueous cigarette tar from mainstream smoke."

"The maximum DNA nicking occurs at a concentration of tar that is equivalent to 1.0 cigarette for ETS tar solutions or 0.24 cigarette for mainstream smoke tar solutions. Thus, ETS tar solutions behave similarly to mainstream smoke tar solutions but are less potent on a per-cigarette basis."

"Because catalase confers at least 90% protection against DNA nicking caused by ETS tar extracts or mainstream tar solutions, we can conclude that hydrogen peroxide is an essential component of the ETS-mediated damage to DNA."

"Glutathione protects against DNA nicking by ETS tar solutions, probably by scavenging oxidants."

"Both ETS tar solutions and mainstream smoke tar solutions bind to and damage DNA by similar mechanisms."

"Clearly, ETS is involved in nicking DNA, and this damage may account for carcinogenic effect of ETS tar."

[3] Bono, R., Arossa, W., Russo, R., Scursatone, E., Castello, D., and Gilli, G., "Environmental Tobacco Smoke and Urinary Cotinine in a Group of Adolescents," *Journal of Environmental Science and Health* A29(7): 1439-1449, 1994 [Issue 86, Item 38]

These Italian researchers report that cotinine data collected in their study can be used to validate a questionnaire about ETS exposure.

EXCERPTS:

"[T]he aim of this epidemiological pilot study was to evaluate the relationship between environmental tobacco smoke exposure and urinary cotinine in 148 subjects randomly chosen from an overall study group of 460. The purpose has been to validate a questionnaire on exposure. Furthermore the Cotinine/Creatinine Ratio (CCR), respiratory function, urinary thiocyanate, and airborne nicotine (ETS) have been measured and the corresponding means are reported."

"For each subject the procedure included: (a) the administration of a questionnaire, (b) the collection of a urine sample, (c) the use of a personal passive sampler, and (d) measurement of the respiratory function."

"Subgrouping of cotinine data was done according to the degree of passive exposure to tobacco smoke deducible from the questionnaire, specifically by the number of cigarettes/day smoked by mother, father, and other cohabitants. In this way, the questionnaire data was [sic] validated using cotinine, the most sensitive marker of dose."

"Data shown in this preliminary report underline a direct relationship between the levels of exposure to tobacco smoke and urinary cotinine. This has been proven showing the difference between the concentrations of cotinine in smokers and nonsmokers and, above all, the difference between the passive smoker groups selected using the questionnaire. This validation will allow the consideration of the answers to the questionnaire relative to tobacco smoke exposure as an independent variable in all the 460 students and for all the parameters analyzed."

"The urine analyses show that these students received some exposure to tobacco smoke (i.e., a mean of 21.42 ng/mL for those 'not exposed'), probably via their limited social life that, excluding the 21-22 hours spent at home or school, largely consists of shopping or sports activities. Twenty-eight of the students studied also had some active exposure from their own smoking habits, ranging from one cigarette per week to five cigarettes per day, and the levels of urinary cotinine in these light smokers are, on average, around 100 ng/mL which is considered the cut-off for determining the light smoking status. In nonsmokers mean urinary cotinine stayed in the narrow range of 20-28 ng/mL."

"In the next paper, the authors will analyze all the data that were collected concerning all the possible assessments of exposure-response relationships. Therefore, it will be possible to compare the complete data that were obtained by the questionnaires, personal air levels of nicotine (ETS), urinary cotinine (and CCR), urinary thiocyanate, and respiratory function."

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[4] **Chan, C.-C., Chen, Y.-C., and Wang, J.-D., "Comparison of Questionnaires, Cigarette Butt Counts, and Nicotine Concentration Measurements in Predicting Schoolchildren [sic] Nicotine Exposure,"** ***Bulletin of Environmental Contamination and Toxicology*** **53: 254-258, 1994 [Issue 83, Item 34]**

The authors of this Taiwanese study report that personal monitoring or measurements of nicotine in living rooms or bedrooms are the only way to estimate personal exposures to ETS.

EXCERPTS:

"In this study, tools of ETS exposure indicators, such as, questionnaire, butt counts and air nicotine concentrations were first evaluated and then applied to estimate schoolchildren's exposure to ETS in Taipei."

"At homes, about 41.9% of children are exposed to ETS. The male parents and grand parents are two main sources of children's ETS exposure at home. Respectively, there are about 37% of homes having a male parent's source, and 29.6% male grand parent's. During commuting, the probability of ETS exposure for children was about 63.8% by taking public bus and 20.1% by using private cars. The cram schools, fast-food stores, and parent's offices are children's three most frequently visited places in the after-school activities. The probability of getting ETS exposure, however, was 10.7% in cram schools, 52.2% in parent's offices, and 60% in fast-food stores. Besides that, children also had 60.8% of time getting ETS exposure in [video] game stores and 36.4% in baby-sitters homes. Among the activities over the weekend, children had a probability of 67.4% getting ETS exposure in cinemas, 64.1% in [video] game stores, and 50% in relative's homes. Even in the outdoor suburban areas, the probability was about 32%."

"As expected, the children from smoker's homes were more likely to be exposed to ETS than those from nonsmoker's homes. The mean personal nicotine exposures were 1.30 ug/m^3 for children living with smoking parents and 0.24 ug/m^3 for children living with non-smoking parents."

"The nicotine concentrations in homes with smokers were about 10 times higher than those in non-smoker's homes. The mean livingroom nicotine concentrations were 2.87 ug/m^3 for homes with smoking parents and 0.24 ug/m^3 for homes with non-smoking parents."

"This model indicated that nicotine concentrations in livingroom increased with the increase butt counts but decreased with the increase in housing ventilation. We also confirmed that nicotine is a very useful indicator of current ETS exposure."

"In conclusion, the impact of ETS on indoor air quality can be estimated by counting cigarette butts and measuring the ventilation conditions in the living rooms in homes with smokers in Taipei in the spring. However, the personal exposures to ETS can only be estimated by measuring nicotine concentrations either at schoolchildren's breathing zones directly, or in his/her living rooms and bedrooms indirectly."

[5] **Coggins, C.R.E., "Expanded Toxicological Evaluations of Aged and Diluted Sidestream Smoke from a Reference Cigarette,"** ***The Toxicologist*** **14(1): 13, 1994 [Issue 85, Item 30]**

This abstract discusses animal research conducted by the R.J. Reynolds Tobacco Co., and concludes that, based on the endpoints studied, there was "no detectable biological activity" of aged and diluted sidestream smoke at concentrations typical of indoor environments.

EXCERPTS:

"Male Sprague-Dawley rats were exposed 6 hours per day, 5 days per week for up to 13 weeks to aged and diluted sidestream smoke (ADSS), used as a surrogate for ETS. The ADSS was presented at a concentration of 0.1 mg particulates/m^3 (typical of indoor environments where smoking is unrestricted), and at 10 and 100-fold exaggerations. . . . The only histopathological response was slight to mild epithelial hyperplasia in the rostral nasal cavity, in the high exposure group only. The severity of the latter change was similar in animals killed after 4, 28 or 90 days (no progression). Increased numbers of DNA adducts were observed in the larynx, heart and lung tissue of animals in the high exposure group only; analyses indicated that the dose-response for DNA-adduct formation was non-linear. All of the observed changes (except DNA adducts, which were substantially reduced) were absent in sub-groups of animals kept without further treatment for an additional 90 days. The end-points used in the study demonstrated that there was no detectable biological activity of ADSS at typical ETS concentrations."

[6] **Crawford, F.G., Mayer, J., Santella, R.M., Cooper, T.B., Ottman, R., Tsai, W.-Y., Simon-Cereijido, G., Wang, M., Tang, D., and Perera, F.P., "Biomarkers of Environmental Tobacco Smoke in Preschool Children and Their Mothers,"** ***Journal of the National Cancer Institute*** **86: 1398-1402, 1994 [Issue 82, Item 37]**

The authors of this study claim that their data suggest that the children of smoking mothers have elevated levels of cotinine (described as a marker of ETS expo-

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sure) and PAH-albumin adducts (described as an indicator of DNA damage).

EXCERPTS:

"The goal of this study was to assess whether levels of cotinine and PAH-albumin were associated with ETS exposure in children and in women of reproductive age, after accounting for background exposures to PAHs in the diet, the workplace, and the home environment. Ethnic differences in biomarkers and the extent to which children's biomarkers are correlated with those of their mothers were also examined."

"Total passive exposure to cigarette smoke was greater among children whose mothers smoked . . . than among children whose mothers did not smoke."

"Both cotinine and PAH-albumin were significantly higher in children whose mothers smoked than in children of nonsmoking mothers. . . . Cotinine levels were also significantly higher in the children of nonsmoking mothers with ETS exposure from other household members and visitors than in the unexposed children of nonsmokers. PAH-albumin did not differ between these two groups."

"Levels of cotinine and PAH-albumin were higher in African-American children than in Hispanic children after adjusting for smoking exposure, as was the case for cotinine in mothers."

"This study demonstrates that ETS exposure of young children via their mothers' smoking is associated with increases in the internal dose of ETS (cotinine) and in the biologically effective dose of the PAH components of ETS (PAH-albumin adducts). Because of the observed correlation between protein and DNA binding by PAH and other carcinogens, albumin adducts indicate that DNA damage is occurring. . . . While maternal smoking was the greatest contributor to these biologic markers in the children, smoking by other household members and visitors was also associated with a significant elevation in children's cotinine levels."

"In the nonsmoking women, total passive smoking in the home (based on self-reported current exposure) was highly correlated with cotinine but not with albumin adducts."

"In this study, albeit using limited measures of dietary, residential, and occupational sources of PAH, ETS was the most important environmental contributor to PAH-albumin adducts in nonsmokers."

"The observed correlation between mothers' and children's cotinine levels within exposure groups could reflect either a familial (possibly genetic) component in this biologic response or common environmental exposures of mothers and children."

"Although the internal and biologically effective doses of tobacco-smoke products, represented by cotinine and PAH-albumin, respectively, were higher in passively exposed mothers than in their children, it is likely that children had less ETS exposure both within and outside the home than their mothers. A limitation of the study was that data on ETS exposure outside the home were not collected, and personal monitoring data on nicotine and PAH air concentrations were not obtained. However, a strength of the study was the detailed information obtained on the level of maternal smoking as well as the level of smoking of other regular household members and regular visitors to the home."

"Although no conclusions can be drawn because of the small sample size, we observed ethnic differences in both cotinine and PAH adducts, with an increase in African-Americans compared with Hispanics. This finding is limited by the small number of measurements in African-Americans."

"In conclusion, to our knowledge this is the first report that young children with relatively light exposure to ETS have elevated levels of both cotinine and carcinogen-protein adducts in their blood. This observation underscores the potential carcinogenic and public health hazard of ETS."

[7] **Letters to the Editor Regarding Domino, E.T., Horbach, E., and Demana, T., "The Nicotine Content of Common Vegetables," *New England Journal of Medicine* 329: 437, 1993 [Issue 83, Item 35]**

The *British Medical Journal* published two letters critical of the claims of Domino, et al., that dietary nicotine could confound measurements of cotinine in body fluids. The letters were by James L. Repace and Martin J. Jarvis, and appeared at *British Medical Journal* 308: 61-62, 1993.

In his letter, Repace, a physicist with the U.S. EPA, claims that Domino's data suggest that a 174 gram serving of eggplant with tomato sauce would produce a 15 ug nicotine dose, if the nicotine did not evaporate during cooking. Repace suggests that most U.S. adults consume about 207 grams of vegetables daily; the eggplant serving would be 84% of this amount. However, he claims, eggplant comprises only 0.4% of the overall vegetable consumption in the U.S. diet. Further, Repace suggests that dietary nicotine would account for 0.7% of a typical nonsmoker's cotinine dose attributable to ETS,

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and thus, could not confound cotinine in body fluids as a marker for ETS.

Jarvis' letter notes that if Domino's claim could be substantiated, it would be an important issue in studies using cotinine as a marker for ETS exposure. He then goes on to suggest, however, that 1 ug of nicotine derived from 244 g of tomato would generate a salivary cotinine level below the limit of detection of the most sensitive assays. Jarvis also claims that his research suggests that children would have to consume 90 kilograms of tomatoes daily to produce the cotinine concentration reported in children with two smoking parents. He concludes: "[W]hile dietary nicotine has curiosity value, it is essentially irrelevant for passive smoking."

[8] **Goth-Goldstein, R., Leadon, S.A., Levine, G., Tischler, A.N., "Indirect and Direct Genotoxic Effects of Main Stream and Side Stream Tobacco Smoke Condensate on Human Mammary Cells in Culture,"** ***Proceedings of the American Association for Cancer Research*** **35: 99, 1994 [Issue 85, Item 31]**

This abstract reports on the experimental exposure of cells to tobacco smoke condensate, and reports that benzo(a)pyrene metabolism was induced, and DNA adducts and thymine glycols were formed.

EXCERPTS:

"The effects of compounds contained in main stream (MS) and side stream (SS) tobacco smoke was studied in normal human mammary epithelial cells (HMEC) . . . The effect of tobacco smoke condensates on the metabolic activation of benzo(a)pyrene (BaP) from its procarcinogenic form to the ultimate carcinogen was investigated. . . . Both MS and SS V [vapor] and P [particle] smoke condensates induced BaP metabolism 2- to 3-fold. This induction can be considered a cocarcinogenic effect, since enhanced activation of BaP does result in increased binding of BaP to DNA. The direct genotoxic effects of tobacco smoke were investigated by incubating cells for 4h to 100 ug/ml of the various smoke condensate fractions and then determining formation of bulky adducts to DNA as well as thymine glycols, which are indicators of oxidative damage to DNA. . . . For both MS and SS smoke condensate, DNA adducts and thymine glycols were formed in a ratio of 1:2. SS smoke condensate was slightly more potent than MS smoke condensate."

[9] **Hecht, S.S., "Environmental Tobacco Smoke and Lung Cancer: The Emerging Role of Carcinogen Biomarkers and Molecular Epidemiology,"** ***Journal of the National Cancer Institute*** **86: 1369-1370, 1994 [Issue 82, Item 38]**

In an editorial accompanying the Crawford, et al., study, the author suggests that studies of biomarkers, such as cotinine and adducts, will be useful in elucidating the claimed relationship between ETS exposure and lung cancer. He states that, at present, it is "not fully established that ETS causes lung cancer," based on epidemiologic data.

EXCERPTS:

"In this issue of the Journal, Crawford et al. report that children of mothers who smoke cigarettes have higher levels of polynuclear aromatic hydrocarbon (PAH)-serum albumin adducts than children of nonsmoking mothers. Certain PAHs, such as benzo[a]pyrene, are well-established respiratory carcinogens. Therefore, this study provides evidence that children exposed to environmental tobacco smoke (ETS) can take up and metabolically activate respiratory carcinogens. . . . Carcinogen biomarkers such as these promise to be important in delineating the role of ETS as a possible cause of lung cancer in nonsmokers. The incorporation of biomarkers into epidemiologic studies potentially can provide greater specificity in linking exposure and disease than conventional techniques. This approach has become known as 'molecular epidemiology.'"

"Establishing cause and effect by conventional epidemiologic studies of ETS and lung cancer has been more difficult. The carcinogen dose received by a nonsmoker exposed to ETS may be only one one-hundredth of that received by an active smoker. Therefore, the risk for cancer will be less, although there may not be a direct relationship between carcinogen dose and risk due to differences in metabolic activation and other factors between active and passive smokers. Conventional epidemiologic studies of ETS and lung cancer have typically found relative risks between 1 and 2. Based on available epidemiologic data, several panels, including the National Research Council, the U.S. Surgeon General, and the Environmental Protection Agency, have concluded that ETS is a cause of lung cancer, with the strongest evidence coming from studies of nonsmoking women exposed to ETS; a recent study has provided further evidence supporting this conclusion. Cotinine has been used as a biomarker in some of these studies. Cotinine is not a carcinogen and its levels in blood or urine will not necessarily provide useful information about carcinogen uptake and metabolic activation.

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Cotinine levels can be used, however, to determine whether recent exposure to ETS has occurred and to prevent misclassification of active smokers as nonsmokers. Overall, conventional epidemiologic approaches (phase I studies) have not fully established that ETS causes lung cancer in contrast to active smoking."

"Carcinogen biomarkers can be used in phase II transitional studies of ETS and lung cancer to bolster the epidemiologic findings. The ideal biomarker, which could perhaps integrate tobacco-specific carcinogen exposure and metabolic activation over a lifetime and provide an estimate of total internal dose of ETS, does not exist. At present, we have to accept substitutes. The detection by Crawford et al. of PAH-serum albumin adducts in the blood of children exposed to ETS supports the connection between ETS and lung cancer by demonstrating that exposed nonsmokers can take up and metabolically activate lung carcinogens, although it should be noted that a link between exposure to ETS in childhood only and lung cancer later in life is unclear. . . . [T]hese findings support the role of ETS as a lung carcinogen; however, further phase II transitional studies using biomarkers will be required to establish more clearly the relationship between ETS exposure and carcinogen uptake and metabolic activation in nonsmokers."

"[T]he application of carcinogen biomarkers in studies of ETS and lung cancer is lagging behind their application in investigations of active smoking and cancer. However, the same strategy applies, and it seems likely that as technology develops, carcinogen biomarkers will increasingly be employed in studies of ETS and lung cancer in nonsmokers. Ultimately, molecular epidemiology is likely to provide the basis for resolving the role of ETS as a cause of lung cancer."

[10] Hovell, M.F., Meltzer, S.B., Zakarian, J.M., Wahlgren, D.R., Emerson, J.A., Hofstetter, C.R., Leaderer, B.P., Meltzer, E.O., Zeiger, R.S., O'Connor, R.D., Mulvihill, M.M., and Atkins, C.J., "Reduction of Environmental Tobacco Smoke Exposure Among Asthmatic Children: A Controlled Trial," *Chest* 106: 440-446, 1994 [Issue 85, Item 32]

In this study, the authors report that parental report of cigarette smoking is a reliable measure of ETS exposure, based on comparisons with data from nicotine monitors. They also report a reduction in exposure associated with parental counseling and monitoring.

EXCERPTS:

"This randomized clinical trial tested a behavioral medicine program designed to reduce asthmatic children's exposure to environmental tobacco smoke (ETS) in the home."

"Families were randomly assigned to an experimental preventive medicine counseling group, a monitoring control group, or a usual treatment control group. Families were measured six times over 1 year."

"The experimental group received a 6-month series of counseling sessions designed to decrease ETS exposure. This group also monitored smoking, exposure, and children's asthma symptoms. The monitoring group did not receive counseling and the usual treatment control group received outcome measures only."

"Parents reported the daily number of cigarettes children were exposed to during the week preceding interviews. A nicotine air monitor and construct validity analysis confirmed the validity of exposure reports."

"The children's mean ETS exposure to their parents' cigarettes was 6.5 (SD=6.6) cigarettes per workday at the baseline home visit."

"The ETS exposure decreased over time for all three groups. Parents in the experimental/counseling group attained a 79 percent decrease in children's ETS exposure. This is in contrast with 42 percent for the usual treatment control group and 34 percent for the monitoring control group."

"For the home ETS monitor, only the time effect was statistically significant. The mean monitor value showed a significant decrease for all groups from the first clinic visit to the final 12-month measurement."

"For children's self-reported 2-week overall asthma and allergy symptom scores, repeated-measures ANOVA showed a significant group-by-time effect at 2 months."

"This analysis is the first to include formal tests for the reliability and validity of parent reports of cigarette smoking and children's ETS exposure. Parent reports were shown to be both reliable and valid measures of ETS exposure in the home."

"Families in the experimental/counseling group attained a significant and clinically important decrease in ETS exposure for their asthmatic children. This decrease was achieved not only for exposure to the target parents' cigarettes, but also for exposure to all cigarettes smoked in the home."

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"From these results it is concluded that motivated parents can report their child's ETS exposure accurately enough for clinical purposes. It is important to note that their accuracy may have been due, in part, to the apparent ability of the investigators to verify their reports by use of the environmental monitor."

"Also of clinical importance is the fact that no objective substitute for the parents' reports of ETS exposure could be used in the administration of the behavioral counseling program. The parents' reported details regarding the timing, location, and activities taking place when the child was exposed were the foundations for counseled change in lifestyle to reduce ETS exposure. Such detailed information could not be obtained by existing objective measures of ETS exposure."

"The mean monitor values depict relatively low ETS levels and a very small decrease across time for all groups, while neither the group nor the group-by-time effects reached significance. These results suggest that the ETS level in the selected room decreased during the course of study. However, no inferences can be drawn from these results regarding the changes in the children's ETS exposure."

"Children assigned to the experimental/counseling group and the monitoring control group reported significant decreases in overall symptoms at the 2-month measurement point which concluded the most intensive counseling period. The decrease was greatest for the experimental/counseling group. These results suggest that health benefits may be attained from the counseling program and even from self-monitoring alone, and support replication with a larger sample in order to provide sufficient power to discover other possible health benefits related to decreased ETS exposure among asthmatic children."

[11] Jaakkola, N., Ruotsalainen, R., and Jaakkola, J.J.K., "What Are the Determinants of Children's Exposure to Environmental Tobacco Smoke at Home?" *Scandinavian Journal of Social Medicine* 22: 107-112, 1994 [Issue 84, Item 31]

In this paper, Swedish researchers report that children's ETS exposure was associated with parental education, and was also more common in children of one-parent families.

EXCERPTS:

"The objective of the present study was to assess the role of smoking parents' educational background, socioeconomic status and knowledge of the child's health as determinants of the child's exposure to environmental tobacco smoke at home."

"The education of smoking parents was observed to be an important determinant of a child's passive smoking. Children of non-professional parents were more than twice as likely to be exposed to ETS than children of parents with college or university education. Socioeconomic status was not essentially related to exposure when adjusting for professional education. However, children of one-parent families were more likely to be exposed than children of families with two parents. The risk of exposure was smaller for atopic children, and asthmatic children were not exposed at all. These results indicate that knowledge of the children's illness affects the smoking behavior of the parents."

"Exposure to environmental tobacco smoke in the home was measured by a parent-administered questionnaire, which may be a source of information bias. The reporting of exposure to ETS rather than the actual exposure could be associated with the determinants of interest."

"Children's passive smoking remains a major public health concern which calls for strong preventative measures. The present results indicate that the resources of health education in the prevention of passive smoking should be focused on single parents and parents with a low educational background."

[12] Ji, C.M., Plopper, C.G., and Pinkerton, K.E., "Induction of P450 Isozyme 1A1 in Developmental Rat Lung Following Exposure to Environmental Tobacco Smoke," *The Toxicologist* 14(1): 13, 1994 [Issue 85, Item 33]

This abstract reports that, in young rats, ETS exposure from birth results in enzymatic changes in the lung.

EXCERPTS:

"P450 isozyme 1A1 is one of the inducible isozymes involved in the bioactivation of procarcinogens present in environmental tobacco smoke (ETS). This study examines the effects of ETS on the development of this protein in the lungs of postnatal rats aged 7 through 100 days. . . . Exposure to ETS from birth significantly increased the expression of 1A1 at all the ages examined. The marked increase was observed in 50 and 100 day-old-rat lung. At 50 days of age, the expression of NADPH reductase, a critical component for the function of the P450 system, was higher in the airways of rats exposed from birth to ETS compared to the controls. Other Clara cell differentiation marker proteins in 50 day-old-rat lungs were not changed by ETS exposure

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from birth. We conclude that, in postnatal rats, exposure to ETS from birth: (1) accelerates and maintains the expression of cytochrome P450 isozyme 1A1 protein in Clara cells during postnatal development; (2) increases the bronchiolar expression of NADPH reductase but does not increase expression of cytochrome P450 isozyme 2B or CC10."

[13] Ji, C.M., Plopper, C.G., Witschi, H.P., and Pinkerton, K.E., "Exposure to Sidestream Cigarette Smoke Alters Bronchiolar Epithelial Cell Differentiation in the Postnatal Rat Lung," *American Journal of Respiratory, Cellular, and Molecular Biology* 11: 312-320, 1994 [Issue 87, Item 38]

Young rats were exposed to aged and diluted sidestream smoke in this experimental study, which reported changes in cellular differentiation in exposed animals.

EXCERPTS:

"This study addresses whether sidestream smoke at a concentration that could be encountered indoors affects the nonciliated bronchiolar epithelial (Clara) cell, a lung cell type that differentiates postnatally and is a primary target for inhaled pulmonary toxicants. The rat was selected for these studies based on the marked growth and development of the lungs in this species during the first months of life. . . . Our primary goals were to examine the impact of ADSS on a variety of functions of Clara cells, including proliferation, maturation, differentiation, and cytochrome P450 isozyme 1A1 expression during critical periods of postnatal development and growth."

"ADSS exposure depressed cell kinetic activity in epithelial cells of terminal bronchioles but not in those of proximal bronchi. ADSS also induced the expression of cytochrome P450 1A1 and NADPH reductase in the Clara cells of both proximal bronchi and terminal bronchioles and, to a lesser extent, in type II cells of the parenchyma, but it did not change the expression of cytochrome P450 isozyme 2B or Clara cell secretory protein."

"An interesting finding of this study was a distinct difference in the age-related decrease in the rate of cell division in proximal bronchi compared with terminal bronchioles during postnatal lung development in normal rats. . . . [T]hese data suggest that the epithelium of proximal bronchi differentiate at a faster rate than epithelial cells in distal bronchioles. . . . Our findings indicate that high cell kinetic activity in normal prenatal animals continues throughout the early postnatal ages and then decreases dramatically to adulthood, when kinetic activity is very low."

"[O]ur finding implies that ADSS exposure may stimulate bronchiolar cell maturation and, therefore, bronchiolar development in the neonatal rat. However, since ADSS contains a wide range of compounds known to damage the epithelium of bronchioles, such as NO_2, another possible explanation for the observed decrease in LIs in the distal airways is that various components of ADSS inhibit the enzymes involved in DNA synthesis or block access to the four nucleotides."

"ADSS exposure increased 1A1 protein expression in Clara cells of rats at all the ages examined but was most marked in older animals (50 and 100 days of age). In both proximal and distal airways, nonciliated bronchiolar epithelial cells showed an increased level of P450 1A1 protein after exposure to ADSS. This increase in protein expression can be traced to two sources: more cells that contain this protein and higher levels of the protein in those cells."

"We conclude that ADSS exposure from birth alters the differentiation of bronchiolar epithelial cells. ADSS exposure accelerates the postnatal decrease of cell kinetic activity in epithelium of terminal bronchioles but not in epithelium of proximal bronchi. Exposure to ADSS from birth accelerates and maintains the expression of cytochrome P450 1A1 protein in Clara cells and type II cells and therefore may increase the capacity for bioactivation of some airborne procarcinogens during the development of the rat lung."

[14] Kemmeren, J.M., van Poppel, G., Verhoef, P., and Jarvis, M.J., "Plasma Cotinine: Stability in Smokers and Validation of Self-Reported Smoke Exposure in Nonsmokers," *Environmental Research* 66: 235-243, 1994 [Issue 85, Item 34]

In this study, plasma cotinine measurements were reportedly higher in ETS-exposed nonsmokers than in nonexposed nonsmokers, although the range of measurements overlapped. The authors suggest that this could lead to exposure misclassification; they also state that a questionnaire about ETS exposure is not a valid means of distinguishing exposed from nonexposed individuals.

EXCERPTS:

"At this moment it is not known whether a single cotinine measurement is a valid indicator of long-term smoking behavior. In the present study therefore, we calculated stability of plasma cotinine levels measured at the beginning and at the end of a 14-week period in smokers in whom smoking behavior was not changed. From these data we calculated how many measurements of plasma cotinine are needed for the correct classification of subjects on their habitual cotinine level. In addition, we report cotinine levels in nonsmokers selected for the

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extent of their exposure to environmental tobacco smoke. Furthermore, we set out to assess the validity of a questionnaire on self-reported passive smoke exposure."

"The ETS-unexposed nonsmokers had no smokers in the home environment. They reported a maximum of 10 hr a week passive exposure to environmental tobacco smoke, with the exception of 4 with between 10 and 20 hr a week. Only 8 had smoking colleagues at work, and these reported less than 10 hr of total passive exposure a week. The ETS-exposed nonsmokers all had one or more smokers in the home environment. Eight reported passive exposure of environmental tobacco smoke between 20 and 40 hr a week, and all others reported at least 40 hr of exposure a week. Except for 10 subjects, all had smoking colleagues at the work place."

"The contrast in self-reported exposure to environmental tobacco smoke was considerable: an average of 4.5 hr a week for the ETS-unexposed group compared to 72.8 hr a week for ETS-exposed nonsmokers. This contrast was reflected in differences in plasma cotinine levels . . . For the ETS-unexposed nonsmokers the mean plasma cotinine concentration was 0.6 ng/ml. For the ETS-exposed nonsmokers the mean was 1.6 ng/ml."

"A single measurement will classify 95% of all subjects within 30% of their 'true' plasma cotinine level. For classification within 10% of their habitual level, nine measurements are needed."

"[T]his study demonstrated that the sensitivity (percentage of ETS-exposed nonsmokers correctly classified) and specificity (percentage of ETS-unexposed nonsmokers correctly classified) for self-reported passive smoke exposure were 56 and 89%, respectively."

"[D]espite a great contrast between the nonsmoker groups, created by selection of the subjects on self-reported exposure, a substantial overlap in cotinine levels between ETS-unexposed and ETS-exposed nonsmokers was observed, resulting in a low sensitivity of 56%. . . . [A] number of subjects will be misclassified according to self-reported passive smoke exposure. It is doubtful if a brief questionnaire about hours of passive smoke exposure is valid to distinguish ETS-exposed from ETS-unexposed nonsmokers."

[15] Nilsen, T., Zahlsen, K., and Nilsen, O.G., "Uptake of Nicotine in Hair During Controlled Environmental Air Exposure to Nicotine Vapour: Evidence for a Major Contribution of Environmental Nicotine to the Overall Nicotine Found in Hair from Smokers and Non-Smokers," *Pharmacology & Toxicology* 75: 136-142, 1994 [Issue 87, Item 39]

Based on exposure of hair samples to nicotine vapor in a chamber, the authors of this paper suggest that airborne nicotine, rather than nicotine from the bloodstream, is a major contributor to levels of nicotine reported in hair of smokers and nonsmokers (*e.g.*, as a suggested marker for ETS exposure).

EXCERPTS:

"In order to make a first step evaluation of the mechanisms involved in an external uptake of nicotine in hair, hair has been exposed to air nicotine vapour in a dynamic nicotine system. Hair nicotine uptake has been studied as a function of exposure time and air concentration of nicotine. Furthermore, the contribution of environmental air nicotine to the overall concentration of nicotine found in hair from smokers and non-smokers has been estimated from measurements of nicotine in hair segments with different distances from the scalp."

"The air chamber concentrations of nicotine selected for the long term exposure study (8 weeks) seem relevant for a long-term human environmental exposure to nicotine. This is based on reports of air nicotine concentrations measured in public places, ranging in mean values from 1.0 to 10.3 ug/m^3, in 44 offices with variable occupancy and ventilation, below 13.8 ug/m^3 and in 10 homes with at least one cigarette smoker, ranging from undetectable up to 20 to 25 ug/m^3 on occasions. . . . As 90-95% of environmental nicotine from tobacco smoke is reported to be in the vapour phase and not in the particulate phase, the chamber exposure experiments performed with nicotine vapour should be relevant for an environmental exposure."

"Earlier studies have anticipated a systemic transport of nicotine and cotinine from blood to the inner hair to be the dominating pathway for hair nicotine and cotinine disposition, making hair nicotine measurement adequate only for revealing the smoking status of the actual individual. The systemic distribution as the major contributor of nicotine to hair is, however, not in line with the findings of an increasing hair nicotine concentration gradient from the scalp and outwards both in smokers and non-smokers."

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"It clearly appears, however, that environmental air nicotine contributes . . . the major part of the nicotine dispositioned in hair."

"Before considering the use of hair nicotine as a biological marker for individual exposure to environmental nicotine, though promising, the relation between nicotine hair uptake and the length and degree of exposure should be further assessed. . . . More studies should also be initiated on the relative contribution of the systemic disposition of nicotine from blood to hair as compared with environmental disposition."

[16] Pessina, G.P., Paulesu, L., Corradeschi, F., Luzzi, E., Tanzini, M., Di Stefano, A., Matteuscci, G., and Bocci, V., "Production of Tumor Necrosis Factor Alpha by Rat Alveolar Marcrophages Collected After Acute Cigarette Smoking," *Archivum Immunologiae et Therapiae Experimentalis* 41: 343-348, 1993 [Issue 85, Item 35]

In this study, the authors report cellular changes in rat lungs exposed to "acute passive cigarette smoking," compared to cells from rat lungs not so exposed.

EXCERPTS:

"[T]he aim of the present study was to investigate the ability of cigarette smoke to activate alveolar macrophages in the lung of rats exposed to an episode of acute passive cigarette smoking and to evaluate the eventual production of cytokines."

"Groups of air-sham-exposed and smoke-exposed rats were examined at various times after exposure. In rats after undergoing smoking of 3 cigarettes for 1 h the blood COHb level was about 16%, that is higher than that obtained in human smokers and in other animals. . . . Immediately after smoking, the total number of alveolar macrophages collected from BAL [bronchoalveolar lavage] was unchanged in respect to that obtained from BAL of control rats, but 8 h after smoking, their number increased significantly. . . . At this latter time and 24 h after smoking we observed also a little increase of PMN [polymorphonuclear cells], probably due to the production by pulmonary cells of some chemotactic factors such as interleukin 8. . . . Our results clearly demonstrated that alveolar macrophages of smoker rats spontaneously released significant amounts of TNF-alpha [tumor necrosis factor-alpha], while AA [antiviral activity] was not detectable."

[17] **Phillips, K., Howard, D.A., Browne, D., and Lewsley, J.M., "Assessment of Personal Exposures to Environmental Tobacco Smoke in British Nonsmokers," *Environment International* 20(6): 693-712, 1994 [Issue 87, Item 40]**

This study, by Hazleton Laboratories in the United Kingdom, discusses residential and workplace ETS exposures, and concludes that the home is the major contributor to exposure. Personal air monitor data, salivary cotinine measurements, and questionnaire data are compared. The study also reports a 16% smoker misclassification rate.

EXCERPTS:

"In this study, the 24-h exposure to ETS of a group of UK nonsmokers was assessed by personal monitoring. Subjects were asked detailed questions about their smoking history and exposure to ETS, and saliva samples were taken for cotinine measurements."

"Subjects were asked to assess their overall exposure to ETS. These assessments could then be compared to measurements made directly using the monitor. Relative contributions from home, work, leisure, and travel to overall ETS exposure were assessed by direct measurements in conjunction with questionnaire information. In addition, spousal smoking, questionnaires, and saliva cotinine levels were compared with personal monitoring as methods of assessing ETS exposure. Comparison of the methods of assessing ETS exposure was also made in order to determine the extent of any correlation."

"From the 327 volunteers recruited for the study, 72 were excluded for various reasons which included 7 who admitted smoking during the monitoring period."

"It is debatable when using saliva cotinine levels what cut-off point should be used when attempting to distinguish between smokers and nonsmokers. . . . In this study, a higher threshold of 25 ng/mL^{-1} was chosen since this would avoid the possibility that some heavily exposed nonsmokers might be incorrectly categorised as smokers."

"It is of interest that a further 12 subjects admitted smoking between recruitment and the 24-h monitoring period.... and yet they were not identified as smokers by their saliva cotinine measurements. This demonstrates that saliva cotinine measurements can fail to identify occasional smokers who have not smoked for a few days and could thus underestimate the extent to which smokers describe themselves as nonsmokers. It is possible that further subjects in this study were occasional smokers, or smokers of low yielding cigarettes, and were not detected."

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"These findings demonstrate that it can be difficult to determine whether a person really is a regular smoker, nonsmoker, or even a casual smoker. This clearly needs to be taken into account in other investigations of ETS exposure."

"In view of the recruitment criteria, it was surprising that 7 subjects admitted smoking during the 24-h monitoring period (questionnaire), 12 subjects admitted smoking since recruitment (questionnaire), and 34 subjects were rejected on the basis of their saliva cotinine measurement. Thus 53, subjects out of a total of 327 (16%) were identified as likely smokers and some of these were clearly regular smokers."

"These results indicate that people from a wide variety of occupations misreport their smoking status, and that misclassification may be more extensive among men (33 out of 150) than women (20 out of 176) in the UK."

"[T]he exposure of most subjects is at the low end of the range. Over 70% of subjects were exposed to less than 10 ug m^{-3} of ETS particles; over 60% were exposed to less than 1 ug m^{-3} of nicotine; and over 60% had saliva cotinine less than 1 ng mL^{-1}."

"Assuming a breathing rate of 1 m^3/h, a person exposed to the median levels found in this study would be exposed to about 1244 mg of PAS, 17.5 mg of ETS particles, and about 4.4 mg of nicotine in a year. This calculation assumes these subjects are exposed at this 24-h median level throughout the year."

"[T]he most heavily exposed subjects would be exposed to approximately 1944 mg PAS, 561 mg of ETS particles, and 63 mg nicotine in a year. This calculation assumes these subjects are exposed at this higher 24-h level throughout the year."

"For comparison, a typical UK cigarette delivers about 12 mg of particles and 1 mg of nicotine to the smoker."

"The data reported here suggest that nonsmoker exposure to ETS in the UK is well below that estimated by Repace and Lowrey for the USA."

"Questionnaire data indicate that, on average, relative contributions to total ETS were subjectively ranked as leisure> work> home> travel, both during the monitoring period and during the last six months."

"[T]he measured exposure levels, based on the means, suggest that the ranking is home> leisure> work> travel."

"It is interesting that the ranking of sources of exposure found by measurement is different from the ranking perceived by the subjects. One possible explanation for this is that subjects have based their judgments on the relative ETS levels in the four situations while taking insufficient account of the time spent in these situations."

"[S]ubjective results indicate that the ranking of exposure is smoking partner> no partner> nonsmoking partner, although there is considerable overlap between individual subjects within the groups. In the group with a smoking spouse/partner, 53% assessed their spouse/partner as their primary source of ETS exposure; 30% assessed work or leisure as their primary source of exposure; and 16% of subjects assessed their exposure as none."

"The measured exposure levels and the saliva cotinine data for these groups suggest the same overall ranking as the subjective data. . . . Furthermore, 29% of subjects with a smoking partner were exposed to less than the mean ETS particle level of subjects with a nonsmoking partner."

"40% of subjects with a smoking spouse/partner have exposure in the lowest SolPM range."

"These findings indicate that a group of subjects with a smoking spouse/partner is likely to have a higher average ETS exposure than a group with a nonsmoking spouse/partner. However, spousal smoking status clearly cannot be used, without supplementary evidence, to assess reliably the ETS exposure of individuals or small groups of subjects."

"Some subjects who reported their exposure as high had less directly measured exposure than other subjects who reported their exposure as low."

"Clearly therefore, an individuals [sic] ETS exposure cannot be reliably assessed by a simple questionnaire."

"Saliva cotinine values showed poor correlation with 24-h ETS particle exposure and, perhaps surprisingly, poor correlation with 24-h nicotine exposure. Some subjects exposed to relatively high levels of ETS particles and nicotine had no detectable saliva cotinine."

"[T]he value of saliva cotinine measurements for estimation of nicotine exposure at low levels must be seriously questioned."

"The results of this study indicate that, for most subjects, exposure to nicotine and ETS particles was close to, or below, the limits of detection of the methods used. These low exposure levels are consistent with the corresponding assessments of exposure made by the subjects, and their saliva cotinine levels. The results are also consistent with other recent studies of ETS exposure by personal monitoring."

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"Overall, this study has shown that it is feasible to assess exposure to nicotine and ETS particles by personal monitoring. This method of assessing ETS exposure would be expected to be more accurate than the saliva cotinine and questionnaire/lifestyle approaches that are sometimes used."

"Since the ETS exposure for most subjects was low and close to the detection limits of the methods used in this study, it would be advisable to improve the precision of measurements at the lowest levels by using a longer monitoring period in future studies."

[18] Pinkerton, K.E., Ji, C.M., Gebremichael, A., Buckpitt, A.R., and Plopper, C.G., "ETS Effects on Perinatal Lung Development in Rats," *The Toxicologist* 14(1): 13, 1994 [Issue 85, Item 36]

Based on experimental exposure of newborn rats to aged and diluted sidestream smoke, the authors of this abstract conclude that ETS exposure is related to cellular and enzymatic changes in the lungs.

EXCERPTS:

"Exposure to ETS in children is associated with increased risks of respiratory disease and cancer. To examine the effects of ETS exposure on lung development, newborn rat pups were exposed to aged and diluted sidestream cigarette smoke (ADDS) as a surrogate to ETS for 6 hours per day, 5 days per week for up to 100 days of age. . . . The incorporation of ^{3}H thymidine in epithelial cells in terminal bronchioles was significantly decreased compared with controls following 7 and 14 days of age. Induction of cytochrome P450 isozyme IA1 was noted as early as 7 days of age and was significantly elevated above control following exposure to ADSS through 100 days of age. Isozyme IA1 was found in nonciliated bronchiolar epithelial cells of the airways. Exposure to ADSS elevated the level of IA1 within nonciliated epithelial cells with striking differences noted at 50 and 100 days of age. Exposure to tobacco smoke was also associated with a 22% reduction in total alveolar tissue mass at 21 days of age and a 24% reduction in total alveolar surface area at 50 days of age. However, by 100 days of age no significant differences were noted in tissue mass or surface area between control and exposed animals. We conclude exposure to ETS significantly depresses epithelial cell kinetics and growth, while increasing cytochrome P450 IA1 activity in the perinatal lung. These changes may play a critical role in the long term effects of ETS on the lungs."

[19] Pletsch, P.K., "Environmental Tobacco Smoke Exposure Among Hispanic Women of Reproductive Age," *Public Health Nursing* 11(4): 229-235, 1994 [Issue 86, Item 39]

Based on questionnaire data from the Hispanic Health and Nutrition Examination Survey (HHANES), the author reports that household ETS exposure occurred for 22-62 percent of women surveyed, and workplace exposure for 22-49 percent.

EXCERPTS:

"This study explored ETS exposure prevalence for Hispanic and Latino women of reproductive age who are a significant and growing, yet understudied, segment of the United States population. Data were analyzed for home and workplace ETS exposure for women age 12-45 who participated in the Hispanic Health and Nutrition Examination Survey (HHANES)."

"Household ETS exposure was reported by substantial percentages of women from all three groups. When all women, regardless of smoking status, were considered across all four age groups, 37% to 63% of Mexican-American, 30% to 63% of Puerto Rican, and 45% to 56% of Cuban-American women reported living with a smoker."

"Nonsmoker ETS household exposure distributions were similar, ranging from 31% to 62% for Mexican-Americans, 22% to 59% for Puerto Ricans, and 40% to 53% for Cuban-Americans. Non-smoker household exposure was significantly higher for adolescents than other age cohorts for Mexican-Americans and Puerto Ricans, 62% and 59%, respectively."

"Workplace ETS exposure was measured for women age 20 and over, so there were no adolescent data. For all women, across the three age groups, 24% to 35% of Mexican-Americans, 26% to 34% of Puerto Ricans, and 33% to 49% of Cuban-Americans worked near a smoker."

"For nonsmokers, 22% to 35% of Mexican-American, 28% to 33% of Puerto Rican, and 33% to 49% of Cuban-American women worked near a smoker. There were no significant exposure prevalence differences across the three age groups."

"Most nonsmoking women are involuntarily exposed to ETS, and changing environmental exposure is important for their health."

"The reasons for the subgroup variation in patterns of exposure could not be determined from this data set. Although the three groups share many cultural charac-

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teristics, they have different countries of origin and migratory histories that could affect health beliefs, behavior, and socioeconomic status. Potential influences on the variation in household ETS exposure are socioeconomic status, family or household constellation, and region of the country. In addition, groups may have different cultural norms about the acceptability of smoking."

"The adolescent ETS exposure data from this study are of particular concern because such high percentages of teenagers reported living with a smoker (54-63%). Adolescents are at risk from two perspectives, the potential health risks from ETS itself and the increased likelihood that they will smoke themselves."

"Even with few such data, women could use a number [of] strategies to reduce household ETS. These include a household agreement on a designated smoking room, not smoking in the presence of children, smoking outdoors only, storing tobacco products outside the house, and having cigarette money come from sources other than general household funds. Addressing exposure reduction from the perspective of a potential harmful effect on children might be effective."

"Objective 3.11 of *Healthy People 2000* focuses on ETS control for work sites. Objective 3.12 focuses on states adopting the indoor clean air act. Workplace ETS exposure for Hispanic women (24-49%) was less than household exposure, but indicated that substantial numbers of women worked near a smoker."

"Although the type of workplace is not known for these subjects, ETS exposure rates suggest the need for further work in the area of smoking policy."

"The Hispanic HHANES data are limited in that the Cuban-American sample was small, and participants were asked only if they lived with a smoker and if they worked near a smoker. No biochemical measures were taken. For household exposure, we do not know who the smoker was, how many smokers lived in the household, how much they smoked, or what type of cigarettes or other tobacco products they smoked. Similarly, for workplace exposure, we do not know the kinds of work environments women were in, how many people smoked, or what smoking materials they used. In addition, workplace smoking legislation enacted in the 1980s could make these data an overestimate of exposure."

[20] Roberfroid, M.B., "Correlating Exposure to Environmental Tobacco Smoke Exposure with Increased Incidence of Lung Cancer in Non Smokers: Is Cotinine a Valid Marker?" *The Cancer Journal* 7: 108-114, 1994 [Issue 84, Item 32]

In this review, the author suggests that a quantitative biomarker, which has yet to be identified, is needed in order to reach a conclusion about the potential significance of low ETS exposures with respect to lung cancer.

EXCERPTS:

"Environmental Tobacco Smoke (ETS) is a complex mixture of Exhaled Mainstream (EMS) and Sidestream Smoke (SS) composed of gases and Respirable Suspended Particles (RSP). It is both a highly diluted and an aged mixture the composition of which is difficult to assess. Based mainly on syllogisms it has been hypothesized that exposure to low levels of ETS increases the risk of lung cancer in nonsmokers. There is no question that nonsmokers living in the presence of smokers are exposed to tobacco smoke constituents. But, to conclude on the significance of such an exposure, in term [sic] of increased incidence of lung cancer in non smokers, can only rely on a quantitative biomonitoring of exposure to agents proven to play a causative role in lung carcinogenesis. [Neither] nicotine nor its metabolites are [sic] likely to be precise markers of exposure to such chemicals. Molecular epidemiology offers a promising, but still to be validated, tool to meet such a challenge by measuring proteins and/or DNA adducts in serum or urine samples."

"The aims of the present paper are:

1) to review the data on the quantitative biomonitoring of exposure to ETS based on nicotine and/or cotinine measurements in physiological fluids.

2) to discuss the relevance of these biomarkers in assessing any increase in lung cancer incidence associated with exposure to ETS.

3) to propose new approaches likely to be more scientifically relevant to evaluate exposure to ETS for risk assessment."

"Of the biomarkers which have, up to now, been developed to a significant stage to monitor tobacco smoke exposure by active smokers, only nicotine and its metabolite cotinine have been used repeatedly to monitor exposure to ETS."

"The general conclusions of these studies are that:

a) the experimental data are not always comparable among different studies, in particular with regard to urinary excretion;

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b) because of its longer half-life, cotinine is likely to be a more suitable marker than nicotine;

c) saliva and urinary concentrations of cotinine correlate with serum concentrations;

d) passive smokers have, in their physiological fluids, concentrations of cotinine equivalent to few ng/ml or ng/mg creatine as compared to hundreds of thousands of ng/ml or ng/mg creatinine in active smokers;

e) such parameters might be valid for estimating acute exposure to relatively high levels of ETS;

f) at low levels of exposure to ETS, non-smokers have concentrations of nicotine and/or cotinine in their biological fluids, which are not very different from those measured in non-smokers not exposed to any identified ETS."

"As a consequence of these differences between MS and ETS, estimates of ETS exposure based on measures of nicotine and/or its metabolite(s) in biological fluids of non-smokers (except perhaps in short-term acute and quite unusual exposure to high dose [sic] of ETS) is [sic] likely to be misleading, at least in terms of increased lung cancer incidence. Furthermore, because of the differences between ETS and MS as well as because of interindividual variations in biodisposition of nicotine, it is difficult to anticipate whether the values will be over or underestimated."

"For ETS to be considered as a risk factor for lung cancer in nonsmokers, calculations should be based on defined exposure to relevant chemicals. Neither nicotine nor its metabolites are likely to be precise markers of exposure to such chemicals which are mainly bound to RSP; whereas nicotine is in the vapor phase of ETS."

"[O]nly the evaluation of the biologically effective dose is likely to allow a correct biomonitoring of exposure to be used for conclusively correlating exposure to ETS with any increased incidence of lung cancer."

"One candidate chemical for such an approach is the aromatic amine 4-aminobiphenyl (4-ABP). Because its concentration is higher (_ 30 times) in SS, it might be a more reliable biomarker for exposure to ETS than nicotine. . . . Available data, although still preliminary, show that the methods are indeed adequate to assay the low levels of adducts found in the biological fluids of non smokers (a few pg/g Hb) and that a relationship might exist between exposure to ETS and the levels of 4-ABP-Hb adducts in non smokers."

[21] Scherer, G., Daube, H., and Adlkofer, F., "DNA Adducts as Biomarkers for Exposure to Genotoxic Substances in Tobacco Smoke," *Journal of Toxicology and Environmental Health* 40: 460, 1993 [Issue 83, Item 36]

The authors of this abstract report on their studies of DNA adducts in smokers, nonsmokers, and persons exposed to ETS. They state that no DNA adducts could be identified in exposed persons that were not also present in unexposed persons.

EXCERPTS:

"DNA adducts are useful biomarkers because they allow detection of an internal dose of a carcinogenic compound at the relevant target organ."

"We investigated the effect of tobacco smoke exposure (both active and passive smoking) on DNA adduct formation in different cells by means of the 32 P-postlabeling assay. . . . [O]nly bulky adducts are detectable."

"We have studied DNA adduct patterns in blood cells (lymphocytes and monocytes), oral mucosa, and placenta and umbilical cord tissues from individuals who smoke, those exposed to passive smoke, and in nonsmoking individuals. In addition, their urine was analyzed for the presence of DNA binding substances by means of an in vitro incubation test containing target DNA and a metabolizing enzymatic system. In only one study did we find additional smoking-related DNA adducts in monocytes from current smokers; its presence could not be confirmed in a second study. When the smokers refrained from smoking for 36 h these adducts disappeared due to the short life span of monocytes (about 8 h). In all the other materials investigated, no DNA adducts could be identified in tobacco-smoke-exposed individuals that were not also present in unexposed persons."

"From these results we conclude that the surrogate cells tested are of only limited value for detecting exposure to genotoxic substances by active or passive smoking."

[22] Spierto, F.W., Hannon, W.H., Kendrick, J.S., Bernert, J.T., Pirkle, J., and Gargiullo, P., "Urinary Cotinine Levels in Women Enrolled in a Smoking Cessation Study During and After Pregnancy," *Journal of Smoking-Related Disorders* 5(2): 65-76, 1994 [Issue 85, Item 37]

This study reports cotinine levels for smokers and nonsmokers. The authors comment that women exposed to ETS for more than eight hours daily had statistically

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significantly higher cotinine levels than did women exposed for less than eight hours.

EXCERPTS:

"We describe the validation of an EIA [enzyme immunoassay] for measuring cotinine in 8,700 urine samples from women enrolled in smoking cessation studies in the three states [Colorado, Maryland, Missouri]. Because the studies took place over a long period (four years) and the specimens were handled by many people, we performed several studies to ensure the stability of the samples and the integrity of the analytical method. We evaluated the stability of cotinine in specimens stored at various temperatures and in specimens repeatedly frozen and thawed; and compared the results of the EIA procedure with those obtained with a GC/MS method. We established the cut-off values discriminating smokers from non-smokers and established levels of cotinine in women smokers and non-smokers during and after pregnancy. Prior to this study, no such values had been reported for such a large study population."

"Table 3 shows the effects that passive inhalation of cigarette smoke and the number of cigarettes smoked have on urine cotinine levels. Note, however, that since more than 20% of the self-reported non-smokers had cotinine values >79 ug/L, we did not include their values in the calculations reported in the appropriate columns . . . T-tests showed that women passively exposed to cigarette smoke for more than 8h/day had statistically higher urinary cotinine levels than those exposed for less than 8h/day. T-tests also showed a significant positive correlation between urinary cotinine levels and the number of cigarettes smoked per day. . . . [u]rinary cotinine levels were significantly higher after delivery than before delivery."

"[W]e estimated that the mean cotinine level was 22 ug/L in the non-smoking population and 1963 ug/L in the smoking population; the cut-off value appears to be approximately 79 ug/L....Also, the cotinine levels...listed for women passively exposed to smoke (17-29 ug/L) appear to be similar to those reported in other studies (7-50 ug/L). It is necessary to repeat, however, that when we calculated cotinine levels in non-smokers' urine, we excluded values which were >79 ug/L from our calculations even if the participant claimed to be a non-smoker. Other investigators have reported that as many as 30% of smokers deny that they actually smoke. In contrast to the high non-disclosure rates by self-reported non-smokers, we found that over 95% of the self-reported smokers had cotinine values greater than 79 ug/L."

"We found that cotinine levels were higher in non-smoking women passively exposed to cigarette smoke than in those not exposed and that cotinine levels increased with increasing exposure. Values obtained by EIA were highly correlated with those obtained by GC/MS. Cotinine levels in women who smoked were higher after childbirth than during pregnancy."

[23] Takenawa, J., Kaneko, Y., Okumura, K., Nakayama, H., Fujita, J., and Yoshida, O., "Urinary Excretion of Mutagens and Covalent DNA Damage Induced in the Bladder and Kidney After Passive Smoking in Rats," *Urological Research* 22: 93-97, 1994 [Issue 85, Item 38]

Based on data from 18 rats, the authors of this study report urinary excretion of mutagens and DNA damage following exposure to sidestream smoke.

EXCERPTS:

"In this report, to gain insights into the relationship between passive smoking and the bladder carcinogenic process, we examined the ability of urine, collected from rats exposed to sidestream smoke of cigarettes, to chemically modify the plasmid DNAs in vitro. We also investigated whether exposure to sidestream smoke induced DNA adducts in the urinary bladder and kidneys of these rats."

"In this study we investigated whether chemicals present in urine after smoking could elicit adducts in DNA in vitro. The plasmid pP-1 DNA treated with urine of rats before smoking showed a radioactive area. This suggested that urine itself contained a component(s) modifying DNA. . . . In 4 out of 6 rats exposed to passive smoking, the urine induced additional spots in the plasmid DNA. The adduct levels in these samples were 17.5 in 10^7 DNA nucleotides. . . . [T]he same chemical(s) present in urine seems to have induced the DNA adduct in vivo, although the identity of the chemical(s) remains to be determined. . . . [T]he concentration of sidestream smoke in the cage was about 10^4-fold higher than that in an actual room with smokers. If a dose response relationship exists between smoke exposure and adduct levels, and if the metabolic pathways leading to cigarette smoke-associated adducts is common to the rat and human, 1-day-inhalation of the contaminated air by the passive-smoker will result in excretion per 24h of urine capable of inducing one adduct in about 10^{10} nucleotides."

"[T]his study has demonstrated that exposure to sidestream smoke of a cigarette causes urinary excretion of mutagens and induces covalent DNA damage in the

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bladder and kidney. [Further] studies are required to explore the role of DNA damage induced by passive smoking in bladder and renal carcinogenesis."

Indoor Air Quality

[1] **Driver, C.R., Valway, S.E., Morgan, W.M., Onorato, I.M., and Castro, K.G., "Transmission of *Mycobacterium tuberculosis* Associated with Air Travel," *Journal of the American Medical Association* 272: 1031-1035, 1994 [Issue 84, Item 33]**

This epidemiologic study examined airline personnel and passengers who had flown with a flight attendant diagnosed with tuberculosis. The authors report that they could document transmission of the tuberculosis bacterium to airline personnel, and perhaps to passengers.

Excerpts:

"[A] flight attendant from a large US carrier had been diagnosed with pulmonary tuberculosis in November 1992. The flight attendant had flown from May through October while symptomatic with cough. Because of concern that the flight attendant may have exposed persons with whom she worked during her flights, an investigation of airline crew members was initiated. Later, based on the results of the crew member investigation, airline passengers were contacted in the second phase of the investigation. In this report, we describe the results of the investigation of tuberculosis infection among airline crew members and passengers after exposure to this crew member with clinically active pulmonary tuberculosis."

"Rates of positive TST results . . . did not differ between contacts exposed within the period May through July and comparisons. However, contacts exposed within the period August through October had significantly higher rates of positive TST results compared with contacts exposed within the period May through July or with comparisons."

"Among contacts exposed within the period August through October, the proportion with positive TST results increased with increasing hours of exposure."

"[A]nalysis showed that the total duration of time exposed to the index case during August through October was the variable most strongly associated with the probability of having a positive TST result."

"Of the 71 frequent flyers identified . . . [the] median duration of exposure was 3.8 hours (range, 1.5 to 6.3 hours). Of the 59 respondents, 24 flew in August, 17 flew in September, and 18 flew in October. . . . Four (6.8%) of 59 were TST-positive . . . All four were on flights with the index patient in October, and none had any other known tuberculosis exposure. . . . [T]he frequent flyers who flew in October were significantly more likely to have a positive TST result than were those who flew in August or September."

"This investigation is the first to show that transmission of *M tuberculosis* occurred in the aircraft environment."

"[A] dose effect of exposure was observed among crew member contacts with positive TST results. All crew member contacts who were TST-positive had at least 11.7 hours of in-flight exposure, suggesting that prolonged exposure was necessary for transmission of infection to crew members."

"Results of investigation of frequent flyers suggest the possibility of transmission of *M tuberculosis* infection to passengers with short exposures under certain circumstances. None of the frequent flyers investigated had more than 6.3 hours of exposure to the index case. . . . [W]e did find a significant association between month of exposure and a positive TST result. This may be related to the fact that exposure in October occurred closer to the time of diagnosis when the index patient had a severe cough and was likely to be the most infectious."

"Manufacturer's specifications of aircraft airflow suggested rapid dilution of infectious particles in a pressurized cabin."

[2] **Hedge, A., Erickson, W.A., and Rubin, G., "The Effects of Alternative Smoking Policies on Indoor Air Quality in 27 Office Buildings," *Annals of Occupational Hygiene* 38: 265-278, 1994 [Issue 84, Item 34]**

Indoor air quality constituents were studied in 27 air-conditioned office buildings which had one of the following smoking policies: smoking prohibited, smoking restricted to separately ventilated rooms, smoking restricted to specially filtered rooms, smoking restricted to areas with no special air treatment, and smoking restricted to offices or workstations. The authors report no significant differences in carbon monoxide, carbon dioxide, humidity, formaldehyde, temperature or illumination associated with smoking policy. They report that smoking policy was associated with respirable suspended particulates, ultraviolet particulate matter, and nicotine.

Excerpts:

"A field experiment was conducted to test the effect of five smoking policies (prohibition and various forms of spatial restriction) on indoor air quality in 17 air-conditioned office buildings."

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"Five smoking policies were selected for investigation: smoking prohibited (SP); smoking restricted to rooms ventilated by a separate ventilation system (RSV); smoking restricted to rooms with local electrostatic air filtration units (RF); smoking restricted to areas with no local air treatment (RNT); and smoking restricted to enclosed offices and open-plan partitioned cubicle workstations (RWS)."

"Smoking policy had a consistent effect on indoor air quality for the pollutants measured, although the concentrations of pollutants generally were low."

"There was no effect on smoking policy on formaldehyde . . . Formaldehyde concentrations were higher in smoking areas than non-smoking areas in the buildings where spatially restricted smoking policies applied, whereas there were no differences among the sites for the SP and RWS policies."

"There was no effect of smoking policy on CO . . . For the spatially restricted policies, CO concentrations were higher in smoking areas than in non-smoking areas. CO concentrations were not significantly different among smoking policies for the office areas."

"There was a significant overall effect of smoking policy on u.v.PM, and concentrations were higher in the areas applying restricted policies than in those applying the SP policy."

"Smoking policy affected $RSP_{3.5}$, because of the significant difference between the SP buildings and all the buildings with restricted policies."

"There were no significant effects of smoking policy on CO_2, temperature, relative humidity or illumination. Analysis of only the spatially restricted smoking policies showed higher concentrations of CO_2 and lower levels of illumination in the smoking areas."

"To test the effects of prohibiting smoking vs allowing smoking on environmental conditions, data for the SP and RWS policies were compared (in SP buildings there was no smoking and in RWS buildings smoking could occur at any desk). No significant differences between the SP and RWS policies were found in concentrations of CO, CO_2, metered RSP or formaldehyde, or in levels of illumination, or temperature or RH, but u.v.PM levels were higher for buildings where the RWS policy was operated."

"The results show that for ETS associated pollutants, ambient indoor air quality in non-smoking office areas in air-conditioned office buildings which spatially restrict smoking can be comparable to that in buildings which prohibit smoking."

[3] Hoge, C.W., Reichler, M.R., Dominguez, E.A., Bremer, J.C., Mastro, T.D., Hendricks, K.A., Musher, D.M., Elliott, J.A., Facklam, R.R., and Breiman, R.F., "An Epidemic of Pneumococcal Disease in an Overcrowded, Inadequately Ventilated Jail," ***New England Journal of Medicine*** **331: 643-648, 1994 [Issue 82, Item 39]**

The authors of this study report that an outbreak of pneumonia in a prison was associated with overcrowding and lack of adequate ventilation.

EXCERPTS:

"In the United States many correctional facilities now operate at far over capacity, with the potential for living conditions that permit outbreaks of respiratory infections. We investigated an outbreak that was identified in an overcrowded Houston jail after two inmates died of pneumococcal sepsis on the same day. Outbreaks of pneumococcal disease have been rare in the era of antibiotics."

"Over a four-week period, 46 inmates had either acute pneumonia or invasive pneumococcal disease due to *Streptococcus pneumoniae* serotype 12F. The jail's capacity had been set at 3500 inmates, but it housed 6700 at the time of the outbreak; the inmates had a median living area of only 34 ft^2 per person. There were significantly fewer cases of disease among inmates with 80 ft^2 per person or more. . . . The attack rate was highest among inmates in cells with the highest carbon dioxide levels and the lowest volume of outside air delivered by the ventilation system (relative risk, 1.94; 95 percent confidence interval, 1.08 to 3.48). Of underlying medical conditions, intravenous drug use was most strongly associated with disease (odds ratio, 4.50)."

"The jail was ventilated by a constant-volume recirculated-air system for central heating, ventilating, and air conditioning that was operating at maximal capacity. Approximately 20 percent of the total volume of air delivered was outdoor air and 80 percent was recirculated air."

"Carbon dioxide levels in 31 cell blocks ranged from 1100 to 2500 ppm (acceptable level, <1000)."

"The engineering design of the jail indicated that the ventilation system would deliver 200 to 500 ft^3 of outside air (median, 260 ft^3) per minute to each cell block. If the capacity of the cell blocks were not exceeded, 12 to 24 ft^3

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per minute would be delivered per person; with the overcrowding, 5 to 24 ft³ [median], 10 ft³) would be delivered per person. The current engineering standard recommends a minimum of 20 ft³ per minute per person."

"Our investigation suggested that a combination of factors was responsible for the outbreak, including host susceptibility, crowding, and ventilation that was inadequate for the number of inmates in the building. . . . *S. pneumoniae* is generally transmitted from person to person by the respiratory route; the association of disease with crowding and poor ventilation in the outbreak described here supports this route of transmission. The movement of large numbers of inmates to court allowed contact between persons from different areas of the jail."

"In the jail building, the variation in the degree of crowding permitted the outside-air supply per person to be correlated with disease rates. Our findings emphasize the importance of designing ventilation systems for correctional facilities that anticipate the possibility of severe overcrowding."

[4] Rogge, W.F., Hildemann, L.M., Mazurek, M.A., Cass, G.R., and Simonelt, B.R.T., "Sources of Fine Organic Aerosol. 6. Cigarette Smoke in the Urban Atmosphere," *Environmental Science and Technology* 28: 1375-1388, 1994 [Issue 84, Item 35]

The authors of this study claim to be able to trace cigarette smoke particulate matter in *outdoor* air. They report that cigarette smoke accounts for 1.0 to 1.3% of the fine particle mass concentration.

EXCERPTS:

"The purpose of the present study is not to add additional knowledge to the extensive literature available for cigarette smoke [composition] and indoor air quality. Instead, in this study, tobacco smoke is viewed as one of the many small sources contributing organic fine particulate matter to the outdoor urban atmosphere."

"In order to trace tobacco smoke particles in a reactive outdoor urban atmosphere that is influenced by a great number of different emission sources, organic marker compounds for tobacco smoke must meet several requirements: The tracer compounds must be (1) source specific, (2) detectable in urban air, (3) exclusively in the particle phase, (4) chemically stable over transport times between the source and the atmospheric measurement sites, and (5) present in known ratio to the traced quantity which in this case is the fine particulate mass concentration increment due to cigarette smoke."

"If nicotine can be detected in urban atmospheric fine particulate matter, it should be viewed as a supportive indication that cigarette smoke indeed is present, while quantification of that cigarette smoke particulate matter should be based on more stable tracers."

"[A]lthough it may be suitable to trace tobacco smoke in indoor environments, solanesol probably is not suitable as a tobacco smoke tracer in the outdoor urban atmosphere."

"A more promising compound class that shows properties similar to the n-alkanes consists of the branched alkanes . . . These . . . show a characteristic concentration pattern in tobacco leaf surface waxes and consequently in tobacco smoke."

"Whether or not cigarette smoke particulates can be traced in the urban atmosphere depends in part on the total emission rates for cigarette smoke constituents. Consequently, the first step is to estimate the emission rates of particle-associated cigarette smoke constituents that have been released during indoor and outdoor activities combined."

"It was shown that the iso- and anteisoalkanes concentration pattern characteristic of tobacco leaf surface waxes is preserved in cigarette smoke particles. To verify whether or not this iso- and anteisoalkane concentration pattern found in the cigarette smoke particles is sufficiently unique that it can be used to trace cigarette smoke emissions in the urban atmosphere, common anthropogenic and biogenic emission sources likewise have been investigated. Particulate matter dislodged from the waxy leaf surfaces of urban plants by wind and weather show on average an iso- and anteisoalkane concentration pattern that is different than that found for the cigarette smoke particles. It was shown that the ratio of iso- and anteisoalkanes to n-alkanes in tobacco smoke is about 40 times larger than that found in the leaf surface abrasion products from urban vegetation. Other major emission sources ranging from vehicular emissions to meat cooking do not show any detectable amounts of iso- and anteisoalkanes."

"Using national cigarette sales data and population data for Los Angeles in 1982, ambient cigarette smoke branched alkane tracer concentrations were estimated that closely resemble concentrations measured in ambient air throughout the greater Los Angeles area. Considering all avenues investigated, the iso- and anteisoalkane concentration pattern found in cigarette smoke particles is unique and is preserved in this urban atmosphere. Atmospheric sampling at an offshore island upwind of

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Los Angeles showed that iso- and anteisoalkanes are below detection limits in the upwind background air. It can be concluded that cigarette smoke particles can indeed be traced in this urban atmosphere, and the tracer assemblage can be used to quantitatively estimate the ambient cigarette smoke concentrations outdoors. On average in 1982 in the Los Angeles area, the outdoor ambient fine particle cigarette smoke concentration determined by this technique averaged approximately 0.28-0.36 ug m^{-3}."

[5] Zock, J.P., Brunekreef, B., Hazebroek-Kampschreur, A.A.J.M., and Roosjen, C.W., "House Dust Mite Allergen in Bedroom Floor Dust and Respiratory Health of Children with Asthmatic Symptoms," *European Respiratory Journal* 7: 1254-1259, 1994 [Issue 85, Item 39]

The authors report that exposure to high levels of dust mite allergen in the bedroom could be an important risk factor for asthma symptoms in children.

EXCERPTS:

"Our present objective was to study the relationship between Der p I levels in bedroom floor dust and peak flow variability, respiratory symptoms and medication intake in children with asthmatic symptoms."

"Der p I levels in dust from carpeted floors were much higher than in dust from hard floors. . . . Because dust mite allergen levels on hard floors were so low, and because several of the more severely asthmatic children had hard floors in their bedrooms as a result of allergen avoidance measures, we were only able to analyse the relationship between dust mite allergen exposure and health outcomes in the children with carpeted bedroom floors. In this group, there were clear positive relationships between dust mite allergen exposure and peak flow variability, shortness of breath, wheeze and attacks of shortness of breath with wheezing."

"The positive correlations between PV [peak flow variability] and respiratory symptoms indicate that measuring PEF [peak expiratory flow] and calculating PV provides an objective indicator for symptoms. Intake of maintenance medication was negatively correlated with PV. This may be due to the fact that these medicines are required to prevent acute symptoms and asthma attacks."

"Our analysis of different cut-off levels indicates that the suggested threshold level of 10,000 ng/g of settled dust as a risk factor for acute asthma may be too high. Even in the relatively small number of children we studied, significant relationships between Der p I exposure and peak flow variability were found at cut-off levels down to 4,000 ng/g. . . . It seems likely that increased peak flow variability and symptoms can be found at even lower levels of exposure in more severely asthmatic children."

"In conclusion, exposure to Der p I found in dust from carpeted bedroom floors appears to increase the severity of asthma in children with a history of asthmatic symptoms."

SMOKING POLICES AND RELATED ISSUES

[1] Benowitz, N.L., and Leistikow, B., "Environmental Tobacco Smoke Hazards and Benefits of Work-Site Nonsmoking Programs," *Western Journal of Medicine* 160: 562-563, 1994 [Issue 83, Item 37]

The authors of this letter summarize reported data on ETS exposure and a number of health endpoints, and claim that these data support worksite and public smoking restrictions.

EXCERPTS:

"On average, nonsmokers with exposure to ETS absorb a dose of nicotine equivalent to actively smoking a sixth to a third of a cigarette per day. Although this may seem like a small amount, such an exposure can be substantial over time. For example, it is estimated that a nonsmoking flight attendant who works international flights where smoking is allowed absorbs the equivalent of 1,000 to 2,000 cigarettes over the course of a career. Some people, particularly small children in poorly ventilated homes and workers in bars or restaurants, may have higher than average levels of exposure. Exposures to ETS at home and at work appear to be additive."

"The means of reducing smoking's adverse occupational effects are increasingly well established. When work-sites are smoke-free, workers have lower levels of heavy or continuing smoking and higher levels of smoking cessation. Many (37%) large California corporations subsidize smoking cessation services (beyond health insurance). The wisdom of these services is becoming accepted, with the demonstration that even a modest participation in work-site smoking cessation programs (or employee time without nicotine patches) reduced absenteeism. Nicotine patches have developed an excellent safety record, and patch supply problems have been overcome."

"An appreciation of the hazards of environmental tobacco smoke is important to practicing physicians for

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several reasons. It provides a basis for advising parents not to smoke when there are children in the home. It provides a basis for insisting that child-care facilities be smoke-free. It provides a basis for recommending smoking restrictions in work sites and other public places. These restrictions at home or at work sites often result in smokers quitting smoking."

[2] **Cannon, L.B., "Passive Smoking in the Royal Navy," *Journal of the Royal Naval Medical Service* 79: 17-21, 1994 [Issue 85, Item 40]**

This paper reports that a survey of a ship's company suggested that the majority were opposed to being exposed to ETS and suggested that reduction of exposure be implemented. The author also suggests that an occupational lung cancer suit could be successfully brought against the Navy.

EXCERPTS:

"Passive smoking is an emotive issue and one which has received considerable coverage in the past few years from both the scientific community and the media. The arguments for and against links between passive smoking and disease are as fiercely contested among members of the Royal Navy as among civilians."

"This article aims to present the current evidence in favour of such a link and also the views on the matter as expressed by the ship's company of a Type 22 frigate. Their views will be compared to the result of a similar survey carried out among civilian workforces. Finally, based on the evidence and results presented, strategies for tackling this problem will be discussed."

"To establish the level of understanding and feelings on passive smoking, the whole ship's company of a Type 22 frigate (HMS *Cumberland*) was given a questionnaire of seven questions to which the response was either yes or no."

"[O]nly 8.4% were unaware of the dangers of passive smoking."

"Smoking restrictions have been adopted among civilian workforces for reasons of health and, perhaps more cynically, for fear of litigation. Several test cases both abroad and in the UK have prompted many employers to take action."

"The type of case that could be successful in the setting of the Royal Navy would be one where a nonsmoker with many years service on ships, develops an oat cell carcinoma, a type of lung cancer with a particularly strong association with cigarette smoking. It could be argued that the cancer was due to a long-term occupational exposure to ETS. Just such a case in a civilian setting has been fought and won -- but not in the UK -- yet."

"The provision of smoke free zones in shore establishments is relatively simple with the majority of buildings relying on natural ventilation. The problem lies with ships that possess integral air-conditioning systems which recirculate 80-90% of the air. Even limiting smoking to designated compartments would not resolve the problem. The smoke filters incorporated into messdecks are only capable of removing a proportion of the 10% of tobacco smoke that is particulate (the remaining 90% containing the noxious gases)."

"The views of a ship's company on passive smoking have been expressed revealing that the majority are opposed to being involuntarily exposed to ETS and would like steps implemented to reduce this. If these results are indicative of the feelings of the rest of the fleet, then it is imperative that the Royal Navy establish definite policies. It should act under its own volition before the decision is forced upon it."

[3] **Rigotti, N.A., Stoto, M.A., and Schelling, T.C., "Do Businesses Comply with a No-Smoking Law? Assessing the Self-Enforcement Approach," *Preventive Medicine* 23: 223-229, 1994 [Issue 84, Item 36]**

Cambridge, Massachusetts businesses were surveyed by the authors of this study, who report that awareness of the city's smoking policy was high, but that compliance with its provisions was "intermediate." They suggest that further efforts to improve compliance be undertaken.

EXCERPTS:

"Many states and cities have adopted laws restricting smoking in public places. Health departments generally regard the laws as self-enforcing, implying little need for monitoring or enforcement. Whether this achieves good compliance at the workplace, a major site of passive smoke exposure, is not known."

"We assessed workplace compliance with a no-smoking ordinance in Cambridge, Massachusetts, by conducting telephone surveys of two stratified random samples of city businesses, 3 and 24 months after the law took effect."

"The worksite provisions require employers to ban smoking in any room 'which employees normally frequent during the course of employment, including, but not limited to, work areas, employee lounges and restrooms, conference rooms, and hallways.' Upon employees' written request, employers may, but are not

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required to, provide an area for smokers, so long as it does not expose nonsmoking employees or the public to smoke. Nonsmokers' preferences are given priority in case of dispute."

"Three months after its adoption, 92% of city businesses were aware of the ordinance, although only 64% knew that it required employers to ban or generally restrict workplace smoking. Awareness of the law declined over the next 2 years as did knowledge of its general provisions."

"The law was initially popular with businesses: 64% favored the law, 16% were neutral, and 20% opposed it at three months. Approval did not change over 2 years."

"Three months after the law, 82% of firms reported having a smoking policy for employees. This fell to 61% at 2 years. Only one quarter of businesses had a written smoking policy at either 3 months or 2 years. The prevalence of worksite smoking *restrictions* and smoking *policies* was the same at 3 months: 83% of worksites reported having smoking restrictions (38% banned smoking and 45% restricted it to designated areas). However, over time smoking restrictions remained constant while smoking policy prevalence fell, so that by 2 years, more firms reported smoking restrictions (80%) than smoking policies (61%)."

"Despite our findings, most respondents considered their business to be in compliance with the law. Three months after its adoption, 202 (70%) of 287 respondents aware of the law considered that it applied to their firm; 171 (85%) of these said that their firm had complied. At 2 years, self-reported compliance had increased. Businesses that felt exempt from the law stated as reasons that they were too small or that no employees smoked; these are not legal exemptions."

"Respondents had few problems complying with the law. At 3 months, no problems were reported by 244 (85%) of 287 firms aware of the law. Customer noncompliance and employee opposition were the problems most often noted. . . . Furthermore, most of the 230 companies aware of the law at 2 years reported that it had had no impact on their costs (n = 233, 97%), revenues (n = 223, 97%), employee productivity (n = 210, 91%), customer complaints (n = 214, 93%), or employee complaints (n = 200, 87%). Eighty-one percent (n = 187) reported no change in air quality, while the rest thought air quality had improved."

"The health department charged with implementing the no-smoking law regarded the law as largely self-enforcing. How successful was this as [an] implementation strategy for the workplace? The high level of awareness and support found initially should have provided a necessary foundation for self-enforcement to work. Did it? The strategy was partly successful. It achieved moderate levels of compliance and cost little, but gaps in knowledge and compliance remained. Despite these gaps, complaints to the health department were few, indicating that complaints are not a valid measure of the extent of noncompliance and that enforcement requires more than just responding to complaints."

"The law's sustained popularity with employers is an important additional finding. Employers aware of the law reported no adverse effects and did not perceive compliance to be burdensome. Not surprisingly, the law was more popular among respondents who did not smoke and in companies with smoking restrictions and few smoking employees."

STATISTICS AND RISK ASSESSMENT

[1] Axelrad, R., Bayard, S.P., and Jinot, J., "Setting the Record Straight: Secondhand Smoke is a Preventable Health Risk," *Tobacco Control* 3: 263-367, 1994 [Issue 86, Item 40]

In this article, the authors, all of whom work for the U.S. EPA, defend the EPA Risk Assessment on ETS against what they describe as tobacco industry criticisms.

EXCERPTS:

"A recent high profile advertising and public relations campaign by the tobacco industry may confuse the American public about the risks of secondhand smoke. EPA believes it's time to set the record straight about an indisputable fact: secondhand smoke is a real and preventable health risk."

"EPA absolutely stands by its scientific and well documented report. The report was the subject of an extensive open review both by the public and by EPA's Science Advisory Board (SAB), a panel of independent scientific experts. Virtually every one of the arguments about lung cancer advanced by the tobacco industry and its consultants was addressed by the SAB. The panel concurred in the methodology and unanimously endorsed the conclusions of the final report."

"The report has also been endorsed by the US Department of Health and Human Services, the National

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Cancer Institute, the Surgeon General, and many major health organizations."

"The finding that secondhand smoke causes lung cancer in nonsmoking adults is based on the total weight of the available evidence and is not dependent on any single analysis. This evidence includes several important facts."

"First, it is indisputable that smoking tobacco causes lung cancer in humans, and there is no evidence that there is a threshold below which smoking will not cause cancer."

"Second, although secondhand smoke is a dilute mixture of 'mainstream' smoke exhaled by smokers and 'sidestream' smoke from the burning end of a cigarette or other tobacco product, it is chemically similar to the smoke inhaled by smokers, and contains a number of carcinogenic compounds."

"Third, there is considerable evidence that large numbers of people who do not smoke are exposed to, absorb, and metabolize significant amounts of secondhand smoke."

"Fourth, there is supporting evidence from laboratory studies of the ability of secondhand smoke both to cause cancer in animals and to damage DNA, which is recognized by scientists as being an instrumental mechanism in cancer development."

"Finally, EPA conducted multiple analyses on the then-available 30 epidemiology studies from eight different countries which examined the association between secondhand smoke and lung cancer in women who never smoked themselves but were exposed to their husband's smoke. Since the epidemiology studies are the major thrust of the tobacco industry arguments against the EPA report, these studies are examined in more detail below."

"The most important aspect of the review of the epidemiology studies is the remarkable consistency of results across studies that support a causal association between secondhand smoke and lung cancer."

"[T]he extent of the consistency defies attribution to chance. When looking only at the simple measure of exposure of whether the husband ever smoked, 24 of 30 studies reported an increase in risk for nonsmoking women with smoking husbands. . . . [N]ine of these were statistically significant, and the probability that this many of the studies would be statistically significant merely by chance is less than *1 in 10 thousand.*"

"When one looks at the 17 studies that examined cancer effects based on the *level* of exposure of the subjects, *every* study found an increased lung cancer risk among those subjects who were most exposed. Nine were statistically significant. The probability of 9 out of 17 studies showing statistically significant results occurring by chance is less than *1 in ten million.*"

"Such exposure-response trends were seen in *all* 14 studies that examined the relationship between level of exposure and effect. In 10 of the studies the trends were statistically significant. The probability of this happening by chance is less than *1 in a billion.*"

"The tobacco industry is raising numerous issues which may distract the public from the fact that secondhand smoke poses a real and preventable health risk. The tobacco industry neither acknowledges nor disputes EPA's conclusions of respiratory effects in children. It focuses instead on EPA's findings on lung cancer."

"The overall thrusts of the tobacco industry's arguments are that EPA manipulated the lung cancer data to come to a predetermined conclusion. The industry also argues that a nonsmoker's exposure to secondhand smoke is so small as to be insignificant. The argument on minimal exposure is belied both by the acute irritation and respiratory effects and the fallacy of the 'cigarette equivalents' approach discussed below. Responses to the specific criticisms of EPA's assessment of the lung cancer data follow."

"Critics of the EPA report argue that by normal statistical standards, none of the 11 US studies included in the EPA report showed a statistically significant increase in the simple overall risk measure, and that EPA should therefore have been unable to conclude that secondhand smoke causes lung cancer in nonsmokers. These critics are misrepresenting a small part of the total evidence on secondhand smoke and lung cancer."

"While the 11 US studies are not, by themselves, conclusive, they do support the conclusion that secondhand smoke is causally associated with lung cancer."

"Critics claim that had EPA not 'excluded' the recent Brownson study, the Agency could not have concluded that secondhand smoke causes cancer. In fact, four new lung cancer epidemiology studies, including the Brownson study, have been published since the literature review cutoff date for the 1993 EPA report, and *all* support EPA's conclusions."

"The 1994 study by Fontham et al of women in two California and three Southern cities is the largest case-control study on the subject ever conducted and is considered by EPA to be the best designed study on secondhand smoke and lung cancer conducted to date."

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"Critics of the EPA report have charged that EPA changed the confidence interval in order to come to a predetermined conclusion. However, the conclusion that secondhand smoke is a known human carcinogen simply does not hinge on whether or not a 95% or 90% 'confidence interval' was used. A confidence interval is used to display variability in relative risk estimates in the epidemiology studies. As discussed above, the group A designation is based on the total weight of the available evidence. The consistency of results that are [sic] seen in the numerous studies examined lead [sic] to a certainty of greater than 99.9% that secondhand smoke increases the risk of lung cancer in nonsmokers."

"Use of what is called in statistics a 'one-tailed test of significance,' which often corresponds to a 90% confidence interval, is a standard and appropriate statistical procedure in certain circumstances. The 'one-tailed test' is used when there is prior evidence that if there is an effect from a substance, it is highly likely to be an adverse rather than a protective effect, or vice versa. . . . EPA used one-tailed significance tests for lung cancer in both external drafts of the risk assessment document as well as the final report. Ninety percent confidence intervals were also used in other EPA cancer risk assessments, including methylene chloride, coke oven emissions, radon, nickel, and dioxin."

"Some critics argue both that the meta-analysis was not an appropriate technique, and that had EPA included the Brownson study (addressed above) in the meta-analysis of overall spousal exposure, EPA could not possibly have classified secondhand smoke as a known human carcinogen. This just isn't true."

"The finding that secondhand smoke is a known cause of lung cancer in humans is based on all the evidence and is not dependent on the meta-analysis of the simple ever- vs never-exposed comparisons, as the critics suggest. If the meta-analysis were removed from the report entirely, the findings would be precisely the same. The meta-analysis was used primarily for estimating and quantifying the population risks from exposure to secondhand smoke, and an alternative approach also used in the report gave very similar results."

"The tobacco industry and its consultants have suggested, for example, that nonsmoking wives might share in the same poor dietary habits as their smoking husbands, increasing their risk."

"The consistency of results across different countries where lifestyle factors, including diet, vary, argues against confounding."

"The EPA report did examine the available data for six potential confounders such as occupation, dietary factors, and history of lung disease, and concluded that none was likely to explain the lung cancer increases seen in the studies."

"Although some have argued that tobacco smoke cannot cause cancer below a certain level, there is no evidence that this threshold exists. . . . The increased risks observed in the secondhand smoke epidemiology studies are further evidence that any threshold for secondhand smoke would have to be at very low levels."

"[T]he cigarette equivalent method has no scientific support, and was rejected by the SAB panel that reviewed the EPA report. Among the many problems with this method is the fact that while secondhand smoke and mainstream smoke contain the same approximately 4000 compounds, their ratios of individual compounds differ by factors in the thousands. . . . An RJ Reynolds newspaper ad, while utilizing the method, acknowledges it may not be relevant for assessing risk from secondhand smoke."

"The tobacco industry frequently argues that because most studies were based on residential exposures, secondhand smoke has not been shown to be a hazard in the workplace. A substance capable of causing cancer in one environment is certainly capable of causing it in any other environment where exposures are comparable, as is the case with residential and workplace exposure to secondhand smoke."

"The RJ Reynolds' media campaign cites a report prepared by the Congressional Research Service (CRS) on cigarette taxes to fund health care reform to argue that CRS believes that the epidemiological evidence on secondhand smoke and health effects is 'weak and uncertain.' However, CRS has not take a position on either EPA's risk assessment or the health effects of passive smoking."

"In EPA's view, the CRS economists' cursory look at the issues is not comparable to the exhaustive analyses and rigorous review process which EPA undertook when examining the extensive database on secondhand smoke and respiratory health. EPA is confident that a comprehensive analysis of the secondhand smoke database by expert scientists from CRS, with adequate peer review, will come to conclusions about the risks of secondhand smoke similar to those of EPA and many other organizations."

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